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Cardiovascular risk factor prevalence, mortality and cardiovascular disease incidence in patients who initiated renal replacement therapy in childhood; systematic review and analyses of two renal registries

Dinara Galiyeva

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The University of Edinburgh

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Declaration

I, Dinara Galiyeva, hereby declare that the thesis has been composed by me and is my own work. This work has not been submitted for any other degree or professional qualification.

Signed:

Date:

Abstract

Background. The incidence of starting renal replacement therapy (RRT) among young people (<20 years of age) in 2013 in Scotland was 7.7 per million (age-related) population. Little knowledge exists about cardiovascular risk factors (CVRFs), long-term survival and cardiovascular disease (CVD) outcomes in patients who initiated RRT in childhood. The main source of routine data for these patients is available from the European Society of Paediatric Nephrology/European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) registry. In Scotland nationally comprehensive data on patients receiving RRT is available from the Scottish Renal Registry (SRR).

Aim and objectives. The overall aim of the thesis is to review relevant literature and conduct retrospective cohort studies describing CVRF prevalence, all-cause mortality and incidence of CVD outcomes in patients who initiated RRT in childhood. ESPN/ERA-EDTA registry data were used to describe the prevalence of anaemia, hypertension, dyslipidaemia and BMI categories and their association with all-cause and CV mortality. SRR data were used to describe all-cause mortality and CVD incidence and their association with age at start of RRT, sex, primary renal disease (PRD), type of RRT and period of start of RRT.

Methods. Systematic searches were performed to identify relevant literature. For the ESPN/ERA-EDTA analyses patients who started RRT between 0 and 20 years of age and who had CVRF data were included. Patients were followed from date of first CVRF measurement until the earliest of death, loss to follow-up, reaching 20 years of age or the end of follow-up (December 31st 2012). Cox proportional hazard models

were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality, comparing patients with and without each CVRF. For the SRR analyses, patients who started RRT under 18 years of age in the period from 1963 to 2013 were included in the analyses. To describe CVD incidence the SRR data were linked to national registers for death and CVD hospital admissions available from 1981 onwards. These analyses, therefore, included patients who started RRT between 1981 and 2013 with follow-up until first CVD event after start of RRT, end of follow-up period or censoring at death. Cox proportional hazard models were used to examine the association of age at initiation of RRT, sex, PRD, type of RRT and period of initiation of RRT with all-cause mortality and CVD incidence.

Results. The systematic reviews revealed a gap in current knowledge about CVD incidence and the association of CVRFs with CVD outcomes in patients who initiated RRT in childhood. In total, 7,845 patients were included in the ESPN/ERA-EDTA registry analysis. The mean age of the patients was 9.5 (SE 0.06) years, 58.9% were male, and the most common PRD was congenital anomalies of kidney and urinary tract (CAKUT). The prevalence of dyslipidaemia, hypertension, anaemia overweight/obesity and underweight was 87.5%, 79.3%, 36.0%, 29.9% and 4.3%, respectively. During median follow-up of 3.7 (IQR 1.7-6.8) years 357 patients died. HRs for anaemia were 2.19 (95% CI 1.64-2.93) and 2.55 (95% CI 1.27-5.12) for all-cause and CVD mortality, respectively. The HR for all-cause mortality for underweight was 1.81 (95% CI 1.30-2.53). No other studied CVRFs were statistically significantly associated with all-cause and CVD mortality.

In total, 479 patients were included in the SRR analyses of all-cause mortality. The most common PRD was CAKUT and 55.3% of patients were male. During a median

follow-up of 18.3 (IQR 8.7-27.0 years) years 126 patients died. Twenty-year survival among patients initiated RRT in childhood was 77.6% (95% CI 73.8-81.3). Age at start of RRT, PRD and type of RRT were significantly associated with all-cause mortality. HR for all-cause mortality for patients who started RRT under 2 years of age was 2.50 (95% CI 1.19-5.25) compared to patients who started RRT at 12 to 18 years old. HR for all-cause mortality for patients with PRD other than CAKUT or glomerulonephritis (GN) was 1.58 (95% CI 1.05-2.39) compared to patients with CAKUT. HRs for all-cause mortality for patients who only received either HD or PD during follow-up were 19.4 (95% CI 10.4-36.4 and 19.5 (9.65-39.7), respectively, compared to patients who received a renal transplant.

In total, 381 patients were included in the SRR analyses of CVD incidence. During a median of 12.9 (IQR 5.6-21.5) years of follow-up after initiation of RRT 134 patients (35.2%) developed CVD. The overall crude CVD incidence was 2.6 (95% CI 2.2-3.0) per 100 person-years. HRs for CVD were 1.69 (95% CI 1.05-2.74) for males compared to females, 1.72 (95% CI 1.02-2.91) for PRD other than CAKUT or GN compared to CAKUT and 8.38 (95% CI 3.31-21.23) and 7.30 (95% CI 2.30-23.16) for patients who only received either HD or PD during follow-up, respectively, compared to patients who received a renal transplant.

Conclusions. This thesis has contributed to knowledge about CVRF prevalence, longer-term survival and CVD outcomes in patients who initiated RRT in childhood by identifying high prevalence of CVRFs and that CVD is a common complication. This study did not investigate whether anaemia, hypertension, dyslipidaemia and obesity are associated with a higher risk of developing CVD after start of RRT. Future research is needed to study whether treatment of anaemia, hypertension, dyslipidaemia

and controlling body weight will reduce the risk of CVD and mortality in patients who initiated RRT in childhood.

Lay summary

The overall aim of the thesis is to describe risk of dying and risk of heart disease in children with kidney failure. I used information collected in the European and Scottish registers of children with kidney failure. I found that risk factors for developing a heart disease, were common in European children with kidney failure. Children with low blood counts or who were underweight were more likely to die than children with normal blood counts or who were normal weight. Just over a quarter of the Scottish children died during the study period. The highest death rates were for children aged less than 2 years when their kidneys failed. Children born with kidney disease and who had a kidney transplant had lower risks of dying and of getting a heart disease than other groups of children with kidney disease. Over a third of children developed heart disease during the study period and the risk was slightly higher in boys than girls. This thesis has contributed to knowledge about heart disease and mortality in children with kidney failure. Future research is needed to study whether increasing blood count, controlling body weight and blood pressure will reduce the risk of heart disease and death in children with kidney failure.

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I dedicate this thesis to my parents, Baurzhan and Yenlik, to my sister Amina and to my nephews, Amira and Aldiyar.

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List of abbreviations

ABPM	Ambulatory blood pressure monitoring
ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
BMI	Body mass index
BP	Blood pressure
Ca	Calcium
CKD	Chronic kidney disease
CKiD	Chronic Kidney Disease in Children
CVD	Cardiovascular disease
CV	Cardiovascular
CVRF	Cardiovascular risk factors
CAKUT	Congenital anomalies of kidney and urinary tract
CI	Confidence interval
CASP	Critical Appraisal Skills Programme Checklist
DG	Dinara Galiyeva
DBP	Diastolic blood pressure
eGFR	Estimated GFR
ESRD	End-stage renal disease

ESPN/ERA-EDTA	European Society of Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
eDRIS	Electronic Data Research and Innovation Service
ESA	Erythropoiesis-stimulating agents
EPO	Erythropoietin
GN	Glomerulonephritis
GFR	Glomerular filtration rate
HD	Haemodialysis
Ht	Haematocrit
Hb	Haemoglobin
HR	Hazard ratio
HDL	High-density lipoprotein
HUS	Haemolytic-uraemic syndrome
IQR	Interquartile range
IPPN	International Pediatric Peritoneal Network
ICD	International classification of diseases
K/DOQI	Kidney Disease Outcomes Quality Initiative

LVH	Left ventricular hypertrophy
MeS	Metabolic syndrome
NHS	National Health Service
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NH	Nynke Halbesma
MARP	Per million of the age-related population
PD	Peritoneal dialysis
PRD	Primary renal disease
PTH	Parathyroid hormone
P	Phosphorus
p/y	Person-years
PBPP	Public Benefit and Privacy Panel for Health and Social Care
RRT	Renal replacement therapy
RCT	Randomised control trial
RR	Relative risk
SE	Standard Error
SD	Standard Deviation
SBP	Systolic blood pressure

SRR	Scottish Renal Registry
SDS	Standard deviation score
TG	Triglyceride
US	United States
USRDS	US Renal Data System
UK	United Kingdom

Chapter 1. Introduction

Chronic kidney disease (CKD) is a serious condition as it can progress to end-stage renal disease (ESRD) which is the final stage of CKD. Treatment with renal replacement therapy (RRT) i.e. dialysis or kidney transplant, becomes necessary to sustain life when a patient reaches the final stage of CKD. The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) registry annually collects data on patients receiving RRT for ESRD from national and regional renal registries in Europe. In 2014, the total unadjusted incidence rate of RRT among all the registries reporting to the ERA-EDTA registry was 133 per year per million of the age-related population (MARP) (1). The incidence of RRT in children and adolescents is much lower than among adults. For Scotland, the ERA-EDTA registry reported the incidence rate of 12.0 per MARP among patients who initiated RRT from zero to 19 years old, while it was 55.1 per MARP for patients from 20 to 44 years old, 143.3 per MARP from 45 to 64 years old, 254.1 per MARP from 65 to 74 years old and 230.8 per MARP for patients older than 75 years old (1).

This "Introduction" chapter defines CKD and describes its classification, aetiology and epidemiology. This chapter also presents the background for this research, and the overall aims and specific objectives of this PhD thesis.

1.1 Definition of CKD in children and adults

The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines define CKD according to the following criteria (2):

1. Kidney damage for a period of three months or more, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), irrespective of the underlying diagnosis; or

2. GFR <60 ml/min/1.73 m^2 for a period of three months or more with or without kidney damage, irrespective of the underlying diagnosis.

Markers of kidney damage include abnormalities in the composition of the blood or urine (microalbuminuria, proteinuria, haematuria), abnormalities in imaging tests (structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests) or pathological abnormalities proven by biopsy test (2).

1.2 Classification of CKD

According to the K/DOQI guidelines (2), CKD in children and adults is divided into five stages, based on the level of estimated GFR (eGFR) with higher stages representing lower eGFR levels (Table 1). The term kidney failure or ESRD refers to an eGFR below 15 ml/min/1.73 m^2. At this level of kidney function, a patient with reasonable life expectancy is generally referred for RRT (dialysis or kidney transplantation) (2).

Table 1. Classification of stages of CKD according to K/DOQI guidelines

Stage	Description	eGFR (ml/min/1.73 m²)
1	Kidney damage with normal or high eGFR	≥90
2	Kidney damage with mild low eGFR	60-89
3	Moderate low eGFR	30-59
4	Severe low eGFR	15-29
5	Kidney failure	≤15

eGFR- estimated glomerular filtration rate

1.3 Methods of assessing renal function

GFR is considered the best marker of kidney function, which can be measured using renal clearance methods. There are several methods to measure GFR. The first method is assessing inulin clearance, which is the gold standard for measuring GFR, in both adults and children. Inulin is an exogenous filtration marker, which is freely filtered, not bound by protein, and is not secreted or metabolized by kidneys. However, this method requires continuous infusions of inulin and collection of timed urine samples using a urinary catheter, which makes it cumbersome and impractical for daily clinical practice (3). The second method to measure GFR is using radioisotopes, such as chromium-51 labelled ethylenediamine tetraacetic acid (51Cr EDTA), and non-radioactive agents, such as iohexol. The plasma clearance of both 51Cr EDTA and iohexol have been shown to correlate well with the renal clearance of inulin (3). However, measuring GFR by using exogenous markers is technically difficult and time consuming. As a consequence, the preferred practice is to use an endogenous marker, such as serum creatinine, which remains the most widely used endogenous filtration marker for GFR estimation (4). Creatinine is a result of the degradation of creatine

synthesised in skeletal muscle (3) and, therefore, is highly dependent on age and muscle mass. Due to this fact, the K/DOQI guidelines advise against the use of serum creatinine alone in the assessment of GFR and, therefore, recommend the use of serum creatinine-based prediction equations for GFR estimation (5).

1.3.1 Estimation of GFR in adults

In adults, the formulas determined by the Modification of Diet in Renal Disease (MDRD) Study (6) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (7) study are used for GFR estimation. However, both formulas have not been validated in patients aged less than 18 years of age (6), therefore, may provide highly inaccurate estimation of GFR (8). Another formula that is used to estimate GFR in adults, the Cockroft–Gault equation can be used in children older than 12 years of age, but not for younger children (8, 9).

Cockroft-Gault=(140-age)(body weight in kg) (0.85 if female)/72x Serum creatinine in mg/dL.

1.3.2 Estimation of GFR in children

The K/DOQI guidelines recommend two formulas for the estimation of GFR in children, the Schwartz (10) and Counahan-Barratt equations (11) (Table 2). Both formulas are based on height and serum creatinine, however, the use of different assays to measure creatinine resulted in different constants cited in the Counahan-Barratt and the Schwartz formula. The Counahan-Barratt formula was developed using a measure of creatinine by an automated method (11), while the Schwartz formula used creatinine measured by a colorimetric reaction with alkaline picrate (10).

Table 2. Estimation of GFR in children using serum creatinine and height

Author	Equation
Schwartz	CCr (ml/min/1. 73m²)= k*Height (cm) / SCr (mg/dL)
Counahan-Barratt	CCr (ml/min/1. 73m²)= 0.43*Height (cm) / SCr (mg/dL)

CCr indicates creatinine clearance and SCr, serum creatinine. In the Schwartz equation, the value k is 0.45 for children <1 year of age, 0.55 for children from 1 to 12 years old and adolescent girls (13-21 years) and 0.7 for adolescent boys (13 to 21 years). In Counahan-Barratt equation, the value k is constant regardless of age at 0.43. To convert serum creatinine from mmol/L to mg/dL, the value should be multiplied by 0.0113.

Although, the estimation of GFR with the Schwartz and Counahan-Barratt equations are more practical for bedside use, these formulae have limitations. They are not recommended to be used in patients in whom height cannot accurately reflect muscle mass, for example in patients with limb amputation, severe obesity or malnourishment. Moreover, they can provide an inaccurate estimation of GFR in critically ill patients and in patients with acute renal failure when GFR is rapidly changing (3). Additionally, both formulae may overestimate the "true" GFR measured by gold standard. In the Chronic Kidney Disease in Children (CKiD) study, conducted in children with CKD stage 2-4, it was shown that the Schwartz equation overestimated GFR measured by the plasma disappearance of iohexol by approximately 12 ml/min/1.73m^2 (12). Moreover, Seikaly et al. reported that overestimation of GFR by the Schwartz formula was most pronounced in advanced stages of CKD (13).

1.4 Renal replacement therapy

There are two options for RRT when a patient`s kidney function fails, which are dialysis or kidney transplantation. Kidney transplantation is generally considered as

the therapy of choice for patients with ESRD, but availability of donor kidneys is limited. Children have a relatively high chance of a transplant due to the fact that a parent is often willing and able to donate a kidney and in most countries children get priority on the waiting list for a deceased donor kidneys. However, a kidney transplantation has often been delayed until the child weights 10 kg or is two years old. The primary reason for this delay is that a kidney transplantation is technically difficult in very young children (< two years old) due to the small size of the child compared to the relatively large (usually adult) donor kidney and the small blood vessel calibre of the recipient (14). Although pre-emptive kidney transplantation i.e. transplantation at the start of RRT, is recommended, in practice this only happens in 10-20% of the children starting RRT (15). Therefore, the majority of paediatric patients receive dialysis while waiting for a renal transplant. Azar describes dialysis as "a procedure that is performed periodically in order to remove excess water from a patient and to cleanse the blood from metabolic toxins. The procedure is done by placing the patient's blood in contact with a dialysate solution across a semi-permeable membrane" (16). There are two forms of dialysis: haemodialysis (HD) and peritoneal dialysis (PD). HD is a procedure in which a patient`s blood is filtered and toxins removed to the dialysis fluid of the HD machine (Figure 1). PD is a type of dialysis, in which excess fluid and toxins are removed from the patient`s blood through the peritoneal membrane of the patient`s abdomen into dialysis fluid. This fluid is then drained through the inserted catheter (Figure 2) (16). Even though the majority of paediatric patients start on dialysis, over time, kidney transplant becomes the most common modality, followed by HD and PD (17). The differences between HD and PD are covered in Table 3.

Figure 1. HD system

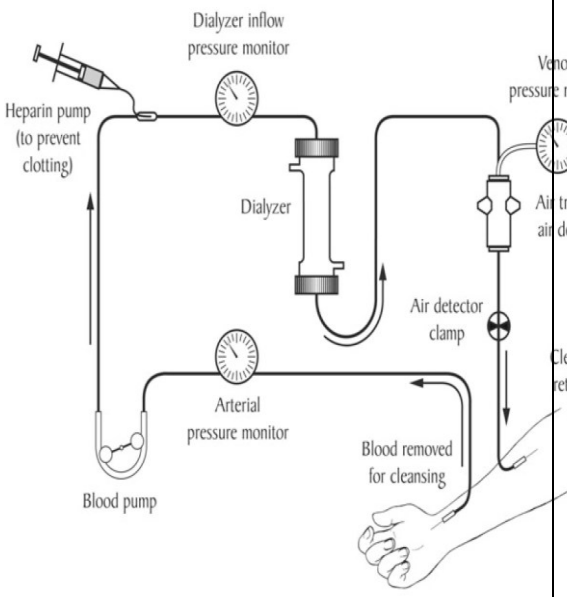
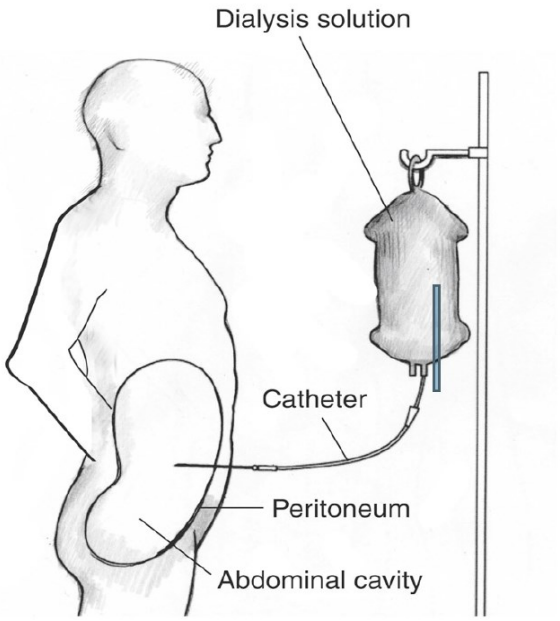


Figure 2. PD system



Source of pictures: Ahmad Taher Azar "Modeling and Control of Dialysis Systems. Volume 1: Modeling Techniques of Hemodialysis Systems. Springer-Verlag Berlin Heidelberg 2013, pages 25 and 29.

Table 3. Differences between haemodialysis (HD) and peritoneal dialysis (PD)

Characteristics	HD	PD
Dialysis characteristics	HD is intermittent. Fluid, wastes and chemicals build up between treatments.	PD is continuous throughout the entire day. Changes in fluid build up and wastes are not so dramatic and noticeable.
Frequency	Usually performed three times a week, but may be up to six times a week.	Dialysis solution is exchanged four to five times every day, or several times during the night.
Duration	Each session lasts four hours if performed three times a week; two hours if performed six times a week.	Each manual exchange of dialysis solution takes 30 to 45 minutes; or 10 to 12 hours during the night using a cycler machine.
Type of access	Requires a vascular access, usually in arm.	Requires a peritoneal catheter inserted in the abdomen
Location	Performed in a dialysis centre or at home.	Many options, usually performed at home or work.

Source of table: Ahmad Taher Azar "Modeling and Control of Dialysis Systems. Volume 1: Modeling Techniques of Hemodialysis Systems. Springer-Verlag Berlin Heidelberg 2013, page 33.

1.5 Epidemiology of patients who initiated RRT in childhood

1.5.1 Sources of paediatric renal data

Most of the existing data on epidemiology of patients who initiated RRT for ESRD during childhood is available from national and international renal registries, mostly from high-income countries. These registries collect information about patients who receive RRT for ESRD. The main source of European data comes from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) registry which was established in 1960 (18). Until 2007 data collection on children and

young adults on RRT in Europe was limited to that of the ERA-EDTA registry. Within the ERA-EDTA registry data are collected from national and regional renal registries. As these do not always include paediatric patients, data on children have only been available from a limited part of Europe. In 2007 an additional registry specifically focusing at children was officially launched. The data collection on children was expanded not only to include more countries, but also to collect much more detailed data on different aspects of RRT. At the end of 2008 this registry was officially named as the European Society of Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA). In 2014, 38 paediatric registries contributed data to the ESPN/ERA-EDTA registry. The majority of the individual European registries cover 100% of the general population of the country, except the Czech Republic, Poland and Russia, which cover 99%, 98% and 99% of the general population, respectively (18). High proportions of countries with national coverage reflects a good generalisability of the ESPN/ERA-EDTA registry to all RRT patients from zero to 20 years of the participating countries.

In the United States (US), data are mainly available from two renal sources: the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry and the US Renal Data System (USRDS) registry. The NAPRTCS was initiated in 1987 to obtain the voluntary participation of all renal transplant centres in the US, Canada, Mexico, and Costa Rica. From 1992, this registry also includes paediatric patients (0-18 years old) who receive HD or PD therapy. Since 1994 this registry also includes data on patients with earlier stages of CKD, defined as eGFR < 75 ml/min/1.73 m^2. Currently, 120 centres in the US, Canada, Mexico, and Costa Rica voluntarily participate and annually provide data to NAPRTCS (19). However, this registry does

not cover complete populations of participating countries, which limits the generalisability of the results obtained by the NAPRTCS if included and not included patients are different.

In contrast to the NAPRTCS, which only receives data voluntarily submitted by paediatric nephrology centres, the USRDS is a national data system created in 1988. The USRDS collects, analyses, and distributes information about all patients receiving RRT for ESRD in the US as participation of renal centres is mandatory. Specific type of analyses such as hospitalizations, costs, and clinical services, are restricted to Medicare patients. Medicare is a federal health insurance program for legal US citizens or legal residents, people 65 years old or older, people of any age with certain disabilities, people of any age with ESRD, requiring dialysis or a kidney transplant (20). However, insurance is not directly available and there is a waiting time of three month until patients become eligible. The USRDS reports that 92% of the patients with ESRD have Medicare insurance, therefore, it is likely that the results of the USRDS have a good generalisability to most RRT patients in the US (17).

Data from Australia and New Zealand are collected by the ANZDATA registry which was established in 1978. The ANZDATA registry collects information on adults and children (0-17 years old) receiving HD, PD and kidney transplantation. All renal units in Australia and New Zealand participate in the registry (21). Therefore, the results of this registry are generalisable to all patients receiving RRT for ESRD in Australia and New Zealand.

The International Pediatric Peritoneal Network (IPPN) gathers information on children and adolescents (0-18 years old) undergoing PD around the world (12 European

countries, US, Canada, Turkey, Chile, Korea, Argentina, China, Finland, Singapore, Finland, Macedonia, Nicaragua, and Uruguay). Participation in the IPPN registry, similarly to the NAPRTCS, is voluntary, resulting in differences in coverage of paediatric PD patients between countries (10% US; 19% Turkey; 31% European countries; 59 % Canada; 80%-90% Chile, Korea, Argentina; 100% China, Finland, Singapore, Macedonia, Nicaragua, Uruguay) (22). Therefore, results may have limited generalisability to those countries with low national coverage, such as the US, Turkey and European countries. Moreover, characteristics of patients in participating countries differ, therefore, the overall results are unlikely to be generalisable.

All of the above described registries collect data on paediatric patients receiving RRT, therefore, do not include patients who have developed ERSD but are not treated by RRT. Therefore, the results of these registries are only generalisable to ESRD patients receiving RRT.

1.5.2 Distribution of underlying primary renal disease in patients who initiated RRT in childhood

The knowledge of distribution of underlying primary renal disease (PRD) in children and young adults receiving RRT primarily comes from national and international renal registries. According to the data from the USRDS, the ESPN/ERA-EDTA and the ANZDATA registries, the main underlying PRD are congenital anomalies of kidney and urinary tract (CAKUT), such as renal hypoplasia or dysplasia, and glomerulonephritis (GN). In a report from the USRDS the leading types of PRD in children and young people (aged 0-21 years) during 2009-2013 were: CAKUT (33.0%) and GN (24.6%) (17). Among patients < 15 years of age starting RRT in 2013

the most common types of PRD reported by the ESPN/ERA-EDTA registry were CAKUT (30%), GN (14.7%) and cystic kidney disease (11.6%) (18). In the ANZDATA registry, the leading type of PRD in children and adolescents (aged 0-17 years) in 2006-2011 were GN (32%), renal hypoplasia or dysplasia (21%) and reflux nephropathy (7%) (21).

1.5.3 Incidence and prevalence of CKD in children

Only a small number of studies have provided information about the incidence and prevalence of the stages of CKD before ESRD in children. For example, an Italian population-based study, conducted between 1990 and 2000, reported a mean incidence of CKD (stages 2 to 4) of 12.1 cases per year per MARP during 1995–2000, with a point prevalence as of January 1, 2001 of 74.7 per MARP in children younger than 20 years of age (23). Another national study was conducted in Swedish children under 18 years of age during 1986-1994. The median annual incidence of more severe stages of CKD (stage 4 and 5) with an eGFR below 30 ml/min/1.73 m^2 was 7.7 per MARP and the prevalence was 21 per MARP (24).

More data are available on the prevalence and incidence of RRT compared to earlier stages of CKD. Data from the USRDS showed that in patients between 0 and 19 years old, the incidence of RRT in 2007 was 14.6 per MARP and the prevalence was 84.6 per MARP (25). The ESPN/ERA-EDTA registry reported that the incidence of RRT in patients aged 0-14 years in Europe was 6.5 per MARP in the 2007 cohort and the prevalence was 33.6 per MARP in 2013 (26). The difference in the reported rates between the US and Europe might be partly explained by the higher proportion of black people in the US, who have a higher risk of developing ESRD compared to white

people (27). Additionally, the incidence and prevalence rates reported by the USRDS were adjusted for age, gender and race, while the ESPN/ERA-EDTA registry reported crude rates.

There is also some knowledge available about the rate of progression to a more severe CKD stage. According to the NAPRTCS registry, 3.5% and 8.6% of children with CKD stage 2 and 3, respectively, develop ESRD within one year following registration, while 43% of all children with CKD stage 4 develop ESRD in the same time period. Younger age, African-American race, focal segmental glomerulosclerosis, hypertension, anaemia, hypocalcemia, hyperphosphataemia and hypoalbuminaemia were significantly associated with a higher risk for progression to ESRD (27).

1.6 Mortality and cardiovascular disease in patients who initiated RRT in childhood

Despite the fact that RRT for ESRD in children and young adults is rare these patients have an increased mortality compared to age- and sex-matched general population. The Australia and New Zealand Dialysis and Transplant (ANZDATA) registry examined the long-term survival of patients who initiated RRT at less than 20 years of age from 1963 to 2002. The results showed that the mortality rate for children receiving RRT was 30 times higher than in the age- and sex-matched general population (28). Cardiovascular disease (CVD) and infection are the main causes of death in patients who initiated RRT for ESRD in childhood. CVD accounted for 20-45% of all deaths in different studies (29-31).

1.6.1. Traditional cardiovascular risk factors

Due to high CV mortality in patients with ESRD, the K/DOQI guidelines for management of CVD in children and adults receiving RRT recommend that "all patients, regardless of symptoms, require assessment for CVD, as well as screening for traditional and non-traditional CVRFs" (32). The prevalence of traditional CVRFs, such as hypertension, obesity, and dyslipidaemia is much higher in patients who initiated RRT for ESRD in childhood compared to age- and sex-matched general population. The prevalence of CVRFs starts to increase in early stages of CKD and continues to persist in ESRD that is demonstrated in the following paragraphs.

Hypertension is one of the most common traditional modifiable CVRF in patients who initiated RRT for ESRD in childhood. Hypertension defined as either systolic blood pressure (SBP) or diastolic blood pressure (DBP) $\geq 95^{th}$ percentile for sex, age and height, is present in 48% of children with CKD stages 2 to 4 registered in the NAPRTCS registry (33), while it is only present in 4.2% (SE 0.7%), 3.3% (SE, 0.6%), and 4.6% (SE, 0.6%) among the general paediatric population of black, white, and Mexican American, respectively, defined as SBP or DBP $\geq 95^{th}$ percentile (33). Hypertension is associated with progression to ESRD (27) and its prevalence is even higher after initiation of RRT. The ESPN/ERA-EDTA registry reported prevalence of hypertension, defined as a SBP or DBP SD scores (SDS) $\geq 95^{th}$ percentile or use of antihypertensive medication, to be 69.7% in HD, 68.2% in PD and 66.5% in transplanted patients (zero to 17 years old) registered in the registry between 1999 and 2010 (34).

Obesity is another important CVRF that is also common in patients who initiated RRT for ESRD in childhood and in earlier stages of CKD. The CKiD prospective cohort study reported that the prevalence of obesity was 15% in children with CKD stages 2 to 4 (35), which is comparable to the prevalence among general paediatric population. Thus, overweight and obesity (body mass index (BMI) for age>85th and >95th percentile) were prevalent in 27.0% and 12.0% of the US children aged 2-5 years, while it was higher in the 6-19 year age group, 33.0% and 18.0%, respectively (36). The prevalence of obesity still persists after initiation of RRT. Obesity was present among 12.5% of all European patients initiating RRT from zero to 15 years old registered in the ESPN/ERA-EDTA registry from 1995 to 2010 (37).

The CKiD study also reported an increased prevalence of dyslipidaemia in CKD patients. The authors reported an increasing prevalence of dyslipidaemia, defined as total cholesterol >200 mg/dl, or high-density lipoprotein (HDL) cholesterol<40 mg/dl, or non-HDL cholesterol >160 mg/dl, with decreasing eGFR. Dyslipidaemia was prevalent in 31.0% of children with eGFR 40-50 ml/min/1.73 m^2, in 53.0% of children with eGFR 30-40 ml/min/1.73 m^2 and 65.0% of children with eGFR less than 30 ml/min/1.73 m^2 (38), while it is lower in the general paediatric population. Overall dyslipidaemia, defined by at least one of the dyslipidaemic measures (hypertriglyceridaemia, or low HDL-cholesterol, or high non HDL-cholesterol), was prevalent among 23% of the US children aged 10-18 years with the most common type being elevated triglyceride (TG) levels (13.2%), defined as TG>130 mg/dl (1.5 mmol/l) (39). The prevalence of dyslipidaemia remains high after initiation of RRT. Dyslipidaemia, defined as TG >100 mg/dL or HDL cholesterol <40 mg/dL, or non-HDL cholesterol >145 mg/dL, was present in 68.0% of patients initiating RRT from

zero to 17 years old and registered in the ESPN/ERA-EDTA registry from 2000 to 2012 (40).

1.6.2. Uraemia-related cardiovascular risk factors

According to the K/DOQI guidelines for management of CVD, another group of CVRFs that needs to be closely monitored is uraemia-related CVRFs that arise from impaired kidney function. Anaemia and abnormal mineral metabolism, defined as abnormal levels of serum Ca, serum P and parathyroid hormone (PTH) are one of the most common uraemia-related CVRFs (32).

The prevalence of anaemia in paediatric patients with ESRD is high compared to the age- and sex-matched general population. Results from the NAPRTCS registry showed that 39.0% of children with CKD stage 2-4 are anaemic, while the prevalence is lower (16.7%) in the general paediatric population in children between zero to five years of age, defined as haemoglobin (Hb) level less than 11.0 g/dl (41). Anaemia has been shown to be associated with increased risk of progression to ESRD. Anaemic patients, defined as haematocrit (Ht) <33%, had a 52% increase in risk of progression to ESRD compared with the non-anaemic patients (hazard ratio (HR) 1.52; 95% confidence interval (CI) 1.36-1.69) (27). Anaemia continues to persist in patients receiving RRT. The ESPN/ERA-EDTA registry reported that the prevalence of anaemia, defined as Hb level less than 11.0 g/dl, is 31.2% in European patients from zero to 18 years old receiving dialysis (42).

Abnormal mineral metabolism is also an important uraemia-related CVRF, which was also shown to be high in early stages of CKD and continues to persist after initiation of RRT. The prevalence of high PTH level was reported to be 47%,

hyperphosphataemia 28% and hypercalcaemia 15% in children with CKD stage 2-4. Abnormal serum Ca and serum P levels has been shown to be associated with progression to ESRD (27). The ESPN/ERA-EDTA registry reported the prevalence of mineral abnormalities among transplanted children; abnormal serum P levels were observed in 25%, altered serum Ca in 30%, and hyperparathyroidism in 41% of patients (43).

1.7 Overall aim and specific objectives of the thesis

In summary, ESRD in children and young adults is a rare condition. Mortality is much higher in these patients compared to the age- and sex-matched general population. CVD is one of the main causes of death and CVRFs are common in patients who initiated RRT for ESRD in childhood. The main aim of my thesis is to describe patterns of CVRFs, all-cause mortality and CVD outcomes in patients who initiated RRT in childhood. Two systematic reviews are performed to identify knowledge about longer-term survival, CVD morbidity and the associations between traditional and uraemia-related CVRFs with all-cause and CV mortality to inform my analyses. Two paediatric renal databases were used for the data analyses: the ESPN/ERA-EDTA registry and the Scottish Renal Registry (SRR), which are described in details in the relevant chapters.

Through a systematic review of the literature and analyses of data from the ESPN/ERA-EDTA and the SRR registries I addressed the following specific objectives of this thesis:

1. To conduct a systematic review to synthesise and critically appraise the relevant published research about the prevalence of traditional and uraemia-related CVRFs and

their associations with all-cause mortality and CVD outcomes in patients who initiated RRT for ESRD in childhood. Hypertension, abnormal BMI, dyslipidaemia and anaemia were the CVRFs addressed in this thesis. The rationale for selecting these particular CVRFs for study are explained in detail in Chapter 2.

2. To describe the prevalence and patterns of traditional and uraemia-related CVRFs and their associations with all-cause and CV mortality in European patients who initiated RRT for ESRD between zero and 20 years of age.

3. To conduct a systematic review to synthesise and critically appraise the relevant published research about long-term survival, CVD incidence and the association of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality and CVD outcomes in patients who initiated RRT for ESRD in childhood.

4. To describe long-term survival, CVD incidence and the associations of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality and CVD incidence in patients who initiated RRT for ESRD in childhood in Scotland.

1.8 Outline of the thesis

Chapter 2 reports a literature review, which consists of two parts. The first is a literature review of the prevalence of CVRFs and the second is a systematic review of the association of CVRFs with all-cause mortality and CVD outcomes in patients who initiated RRT for ESRD in childhood. Chapter 3 describes the ESPN/ERA-EDTA registry data analyses of the prevalence of CVRFs and their association with all-cause and CV mortality. Chapter 4 presents a literature review of survival, CVD outcomes and the associations of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality and CVD outcomes in patients who initiated RRT for

ESRD in childhood. Chapter 5 and 6 are the SRR registry data analyses of all-cause mortality, survival, CVD incidence and the association of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality and CVD incidence. Chapter 7 is an overall discussion and conclusion chapter, which highlights the main findings, limitations and strengths of the current thesis. Additionally, it provides recommendations for future research and implications of the current findings for clinical practice.

Chapter 2. Prevalence and patterns of cardiovascular risk factors and their association with all-cause mortality and cardiovascular disease outcomes in patients who initiated RRT for ESRD in childhood; literature review

2.1. Introduction

CVD is one of the main causes of death in patients who initiated RRT for ESRD in childhood. The ESPN/ERA-EDTA registry reported that CV mortality was the main known cause of death (25.8%), followed by infection (17.0%) and malignancies (5.2%). However, the cause of death was missing in 26.1% of cases. The most common cause of CV death was cardiac arrest/sudden death (54.4%) (30).

Previous studies showed a high prevalence of hypertension (44, 45), dyslipidaemia (46), obesity (47) and anaemia (48) in patients who initiated RRT for ESRD in childhood. It was also shown that these CVRFs start to occur from the early stages of CKD (49-52). Moreover, hypertension (53), obesity (54) and anaemia (55) were reported to be associated with higher risk of all-cause mortality in this specific population.

Although the prevalence of CVRFs and their association with all-cause mortality in patients who initiated RRT in childhood has been described previously, the existing studies vary in the choice of study design and their selection of study participants. The results of some studies may suffer from selection bias that can lead to over- or underestimation of the effect. Furthermore, the information about the prevalence of different combinations of traditional and uraemia-related CVRFs is uncertain.

Several systematic reviews have been conducted in adult RRT populations. These generated the results that point to the association between Hb level and all-cause mortality (56, 57) and the association of BMI with risk of cardiac disease (58) and all-cause mortality (59). However, no systematic reviews have yet been performed in patients with childhood-onset RRT that summarises and critically appraises results of the association between CVRFs and all-cause mortality and CVD outcomes.

This literature review aims to identify, critically appraise and synthesise the relevant published research about the prevalence of single and multiple CVRFs and their association with all-cause and CV mortality and CV morbidity in patients who initiated RRT in childhood.

The specific objectives of this literature review are:

1. To identify, synthesise and critically appraise information about the prevalence of individual and multiple CVRFs in patients who initiated RRT in childhood.

2. To identify, synthesise and critically appraise evidence for associations between individual CVRFs and all-cause mortality and/or CVD outcomes in patients who initiated RRT in childhood.

The following CVRFs are considered in this literature review: hypertension, obesity, dyslipidaemia and anaemia.

2.2 Methods

A protocol for the systematic review was published in PROSPERO, an online prospective register of systematic reviews. Registration number: CRD42015024428. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015024428

2.2.1 Search strategy

A literature search strategy was designed primarily to identify studies that were reporting associations of CVRFs with all-cause mortality and CVD outcomes. From the results of this search strategy I also identified studies reporting only the prevalence of CVRFs that did not report association of CVRFs with all-cause mortality and CVD outcomes. When the search was oriented on the prevalence of CVRFs it yielded over 30,000 results. I had, therefore, chosen the above approach to yield a more manageable number of papers. Since the search for the prevalence of CVRFs was not systematic, it is a literature review. Therefore, this literature review is presented in two parts:

1. The first part is a literature review that describes and critically appraises the information about the prevalence of CVRFs in patients who initiated RRT in childhood.

2. The second part is a systematic review, which describes and critically appraises the studies reporting the associations between CVRFs and all-cause mortality and/or CVD outcomes (CVD morbidity and CVD mortality) in patients who initiated RRT in childhood.

At my first year PhD review I was advised to limit the search strategy to hypertension, obesity, dyslipidaemia and anaemia. This is because preliminary literature searches performed in the first year of my PhD found no studies describing the association between abnormal mineral metabolism and all-cause mortality and CVD outcomes. Therefore, search terms for abnormal serum Ca, serum P and PTH, were not included in the search strategy. Nonetheless, this information was extracted and included in the

literature review from the identified studies. Other traditional CVRFs, such as diabetes and smoking, were not addressed as they are uncommon in children.

Medline (1946 - July week 2, 2015) and Embase (1980 - July week 2, 2015) electronic literature databases were searched, using a comprehensive search strategy comprised of Medical Subject Heading terms and keywords for renal disease, CVRFs and the outcomes of interest (see Appendix 1, page 351). The reference lists of relevant articles were also perused to identify additional relevant references. Furthermore, annual reports of the national and international renal registries (the ERA-EDTA, the ESPN/ERA-EDTA, the USRDS, the NAPRTCS, the ANZDATA, the United Kingdom (UK) and the SRR registries) were searched.

2.2.2 Inclusion and exclusion criteria for study identification for this review

Inclusion criteria for literature review

Randomised clinical trials (RCTs) and observational studies that included patients who initiated RRT for ESRD in childhood and that reported prevalence of anaemia, obesity, hypertension, and dyslipidaemia were included.

Exclusion criteria for literature review

Studies that reported prevalence of anaemia, obesity, hypertension, and dyslipidaemia in patients with adult-onset RRT for ESRD were excluded.

Inclusion criteria for systematic review

RCTs and observational studies among patients who initiated RRT for ESRD in childhood and that reported the association of anaemia, obesity, hypertension and

dyslipidaemia with all-cause mortality and CVD outcomes (fatal and/or non-fatal) were included.

CVD outcomes in this systematic review included: endocarditis, heart failure pericarditis, coronary artery disease; cardiomyopathy; cardiac arrest; valvular heart disease; arrhythmias; myocardial ischaemia, stroke, and peripheral vascular diseases such as thrombophlebitis. Congenital heart defects such as aortic coarctation, trilogy of Fallot, tricuspid atresia or tetralogy of Fallot were not included in this review.

Exclusion criteria systematic review

Studies that reported association of CVRFs with CV surrogate end-points (left ventricular hypertrophy (LVH), carotid intima-media thickness, coronary artery calcification or coronary intravascular ultrasound plaque volume) that were obtained from non-invasive imaging techniques were excluded. Studies that included patients with adult-onset RRT for ESRD were excluded.

Both parts of the literature review excluded studies that were not written in English.

2.2.3 Data extraction and assessment of risk of bias and confounding

A single author - Dinara Galiyeva (DG) - screened the results of the search strategy to identify relevant studies for inclusion, first by abstract and then by full text. Data from relevant full-text studies were extracted for both parts of the review by DG. Data extraction tables were used to extract the following information from each study: author/s; year of publication; data sources and settings; study population; length of follow-up; definition of exposure; incident/prevalent RRT population; statistical techniques used; and results of the study analysis (crude/adjusted effect estimates and

CIs). Authors were contacted where necessary to request additional information that was lacking in the original paper.

95% CIs were calculated around reported prevalence estimates using the following formulas:

Standard error of the proportion (SE) $=\sqrt{[P \times (1 - P)]/N}$, where P-proportion, N total number of patients

$95\%\ CI = P \pm 1.96 \times SE$

Since the aim is to publish the results of the systematic review, a second author Nynke Halbesma (NH), who is a co-supervisor of my PhD, was allocated. NH compared my extracted data against the articles included for the systematic review. DG and NH independently assessed the risk of bias and confounding factors in the included studies using the Critical Appraisal Skills Programme (CASP) checklist (60). Disagreements between authors over the extracted data and risk of bias and confounding were resolved by discussion, with no need to consult a third reviewer.

The CASP checklist was chosen for assessment of the included studies because of its conceptual approach for assessing validity of the studies. The questions are organised to cover all three main epidemiological concepts of study assessment: conceptual validity, internal validity and external validity of the studies. This makes it easy to follow the structure of the questionnaire.

The result of the literature and systematic reviews were summarised in a narrative synthesis since studies differed in terms of RRT population and methodology, so it was not feasible to pull the results together in meta-analysis. A meta-analysis is a

statistical technique that allows results from individual studies to be combined to give an overall measure of the effect (61).

PRISMA guideline was used for reporting this literature review. A checklist of features that were followed and not followed are included in the Appendix 1, page 379

2.3 Results

The flow diagram of included and excluded studies is presented in Figure 3. In total, after excluding duplicate records, 9,365 records were identified through two database searches. After screening titles and abstracts 8,188 records were excluded, leaving 1,177 relevant papers for full-text review. Ultimately, 1,155 full-text articles were retrieved and assessed for eligibility and 41 studies were included in this literature review. Thirty-eight studies were included in the literature review and seven studies were included in the systematic review. The combined number adds up to more than 41 since some studies were included in both literature and systematic reviews[1]. Characteristics of 41 studies included in the literature and systematic reviews are presented in Table 4 (in the table the number in superscript refers to the study

[1] Thirty-four studies were included exclusively in the literature review since they reported only the prevalence of CVRFs. Three studies were included exclusively in the systematic review since they reported only the associations of CVRFs with outcomes of interest without reporting the prevalence of CVRFs. Four studies were included in both parts of the review since they reported both prevalence of CVRFs and their association with outcomes of interest.

identifier). Studies in this table are organised by the year of publication in ascending order. Studies generally included patients up to 18 years of age. All studies reported a higher proportion of male patients compared to female. The most common underlying renal disease was CAKUT. Not all studies reported the distribution of race/ethnicity in their study population. The studies that did report race distribution showed that the population was predominantly white.

Among 38 studies included in the literature review the prevalence of hypertension was described in almost half (19 studies) of the included studies. Ten studies were included for the prevalence of dyslipidaemia, nine for obesity, 10 for anaemia and three for abnormal mineral metabolism. Eight studies described prevalence of several CVRFs in the same study population and as a result papers are used in more than one section[2].

2.3.1 Characteristics of the studies included in the literature and systematic reviews

Out of 38 studies included in the literature review 24 articles were single-centre and 14 were multi-centre studies. Twenty-six studies included only patients after kidney transplantation. Nine studies included patients receiving HD or PD and three studies included both dialysis and transplanted patients. Twenty-five studies were cross-sectional - a type of observational study that examines the relationship between diseases (or other health outcomes) and other variables of interest as they exist in a defined population at one particular time (62). Thirteen studies were cohort studies. A cohort study is an observational study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed –or

[2] The final number of included studies in the literature review adds up to more than 38.

exposed in different degrees-to a factor or factors hypothesised to influence the occurrence of a given outcome (62). The combination of multiple CVRFs was described by three studies.

All seven studies included in the systematic review were observational cohort studies, with no RCTs identified. Three studies reported associations with all-cause mortality for anaemia, two for BMI and two for hypertension. Only one study described the association between hypertension and cerebrovascular mortality. Six studies used data from national or multi-national renal registries and one was a single-centre study. Three studies included patients receiving dialysis, two studies included patients after kidney transplantation, two studies included both dialysis and transplanted populations and one study included patients with CKD stage 1 to 5.

Figure 3. Flow diagram of included studies of the prevalence and patterns of CVRFs and their association with all-cause mortality and CVD outcomes in patients who initiated RRT for ESRD in childhood identified from Medline (1946-2015) and Embase (1980-2015)

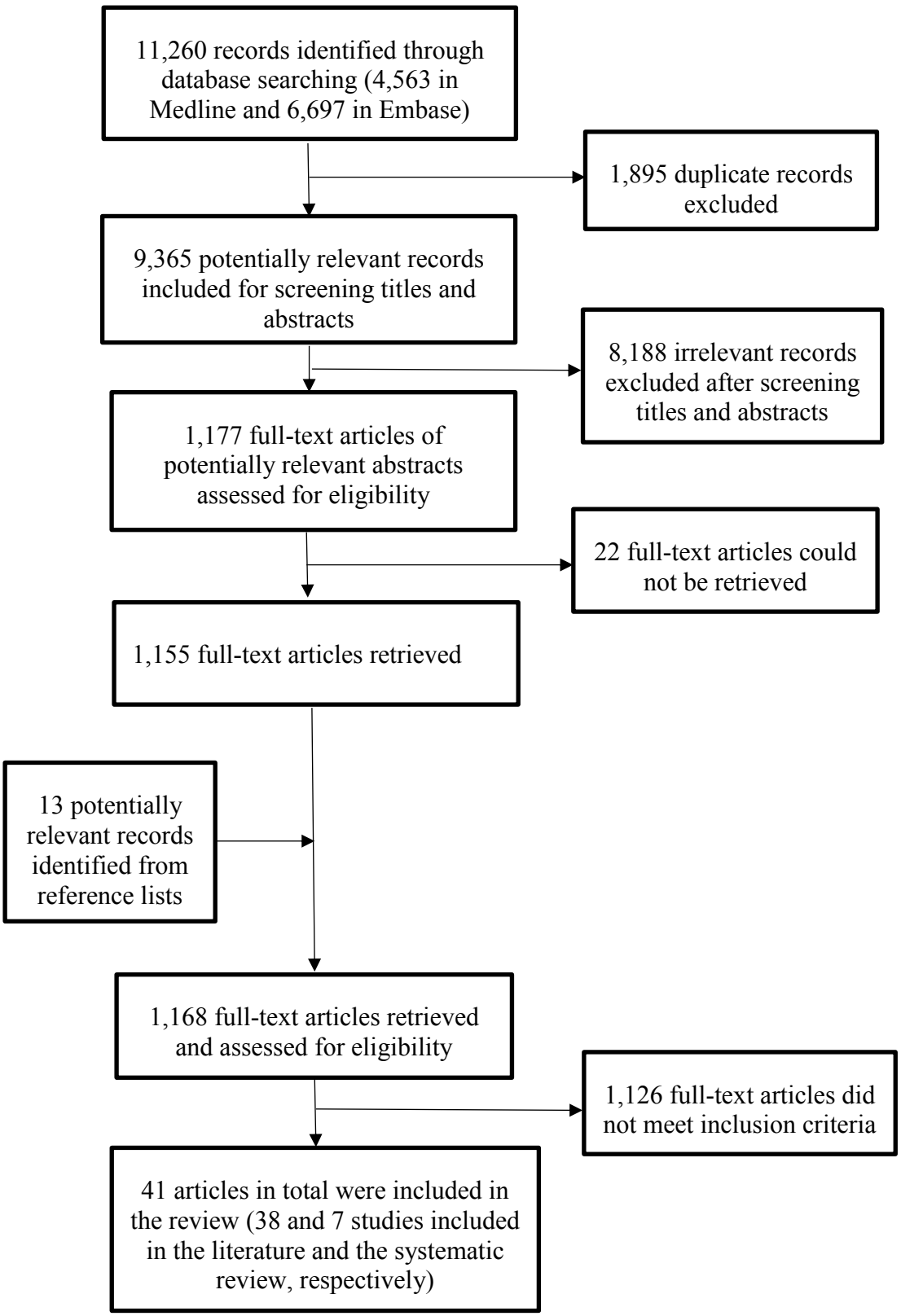


Table 4. Study characteristics of included studies in the literature and systematic reviews reporting the prevalence of CVRFs and their associations with all-cause and CVD mortality in patients who initiated renal replacement therapy for end-stage renal disease

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
Baluarte et al. (1994)[95]	NAPRTCS, (USA, Canada, Mexico and Costa Rica)	Cross-sectional	277 (123)	Tx	Incident	Range 0-18	61.0	NR	CAKUT 37.0 GN 5.0 FSGS 7.0 Other NR	LR (hypertension)
Silverstein et el. (2000)[99]	Louisiana State university medical centre, USA	Cross-sectional	62 (NR)	Tx	Prevalent	15.4 (4.7)	73.4	Caucasian 77.4 Black 22.6	CAKUT 48.4 FSGS 16.0 GN 6.5 HUS 6.5 Cystic kidney disease 6.5 Other 22.6	LR (dyslipidaemia)
Wong et al. (2000)[107]	USRDS 1990-1996, USA	Cohort	1,949 (36)	HD, PD, Tx	Prevalent	Range 0-18	59	White 75.3 Black 19.4 Other 5.3	CAKUT 36.4 GN 26.0 Vasculitis 11.4 Other NR	SR (association of BMI with all-cause mortality)
Groothoff et al. (2002)[53]	National Dutch Registry of patients on RRT, The Netherlands	Cohort	249 (no patients with missing data)	HD, PD, Tx	Incident	Mean 10.6 (range 1.9-14.9)	55	NR	NR	SR (association of hypertension with all-cause and cerebro-vascular mortality)

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
Yorgin et al. (2002)[65]	Children`s hospital, Stanford, USA	Cohort	162 (4)	Tx	Incident	11.5 (6.1)	63.0	White 51.2 Hispanic 27.1 Black 6.7 Asian 3.1 Pacific Islander 5.5 Other 6.1 Unknown 0.3	CAKUT 54.3 GN 27.1 HUS 3.1 Metabolic disease 3.7 Other 11.8	LR (anaemia)
Mitsnefes et al. (2002)[77]	Children`s hospital medical centre, Cincinnati, USA	Cohort	89 (13)	Tx	Incident	13.5 (5.3)	60.0	White 83.0 Black 17.0	CAKUT 41.0 GN 43.0 Cystic disease 8.0 Other 8.0	LR (obesity)
Chavers et al. (2003)[100]	University of Minnesota medical centre	Cohort	59 (19)	Tx	Incident	8.2 (5.7)	59.0	White 83.0 Black 5.1 Hispanic 6.8 Other 5.1	CAKUT 52.5 GN 11.9 Nephrotic syndrome 18.6 Other 17.0	LR (dyslipidaemia)
Mitsnefes et al. (2003)[84]	Cincinnati Children`s Hospital Medical Centre, USA	Cross-sectional	159 (56)	Tx	Prevalent	12.9 (4.8)	63.0	White 88.0 Black 12.0	CAKUT 63.0 Acquired 30.0 Metabolic 7.0	LR (hypertension)
Warady et. al (2003)[71]	NAPRTCS registry, 1992 -	Cohort	1,942 (no patients	HD and PD	Incident	10.3 (range 0-17)	56.4	White 51.2 Black 24.2	CAKUT 39.9 GN 16.4	LR and SR (prevalence of

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
	2001, US, Canada and Mexico		with missing data)					Hispanic 18.4 Other 6.2	FSGS 14.6 Other 29.1	anaemia and its association with all-cause mortality)
Kitzmueller et al. (2004)[87]	Single centre, Vienna, Austria	Cross-sectional	39 (NR)	Tx	Prevalent	10.6 (4.8)	NR	NR	NR	LR (hypertension)
Kausman et al. (2004)[70]	Royal Children`s Hospital , Australia	Cross-sectional	50 (no patients with missing data)	Tx	Prevalent	13.5 (5.2)	58.0	NR	CAKUT 56.0 GN 10.0 Nephronophthisis 10.0 HUS 4.0 Cystic kidney disease 2.0 Other/unknown 18.0	LR (anaemia)
Mir et al. (2005)[88]	Paediatric nephrology transplantation centre, Izmir, Turkey	Cohort	72 (no patients with missing data)	Tx	Prevalent	13.2 (3.7)	45.0	NR	CAKUT 27.7 GN 20.9 Chronic pyelonephritis 16.6 FSGS 15.3 Other 15.3 Unknown 4.2	LR (hypertension, dyslipidaemia)

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
Mitsnefes et al. (2005)[67]	Cincinnati Children`s Hospital, USA	Cohort	301 (65)	Tx	Prevalent	12.6 (5.0)	59.0	White 80.5 Black 18.0 Other NR	CAKUT 53.0 GN/FSGS 39,.0 Other 8.0	LR (anaemia)
Hanevold et al. (2005)[54]	NAPRTCS registry, 1987 - 2002, US, Canada and Mexico	Cohort	6,658 (NR)	Tx	Incident	4.3 (SD not reported)	59.0	White 61.0 Black 16.0 Hispanic 17.0 Other 6.0	CAKUT 52.0 Other groups NR	LR and SR (prevalence of obesity and its association with all-cause mortality)
Amaral et al. (2006)[72]	Centres for Medicare and Medicaid Services ESRD CPM Project, USRDS, 1999-2003, USA	Cohort	677 (no patients with missing data)	HD	Prevalent	16 (1.7)	52.0	White 49.0 Black 41.0 Other NR	CAKUT 41.0 Other NR	LR and SR (prevalence of anaemia and its association with all-cause mortality)
Bullington et al. (2006)[66]	Cintinati Children`s Hospital, the US	Cross-sectional	47 (21)	Tx	Prevalent	13.6 (5.2)	52.0	White 76.0 Black 24.0	CAKUT 52.0 Acquired 48.0	LR (anaemia, hypertension)
Becker-Cohen et al. (2006)[68]	Paediatric nephrology unit at the medical centre,	Cross-sectional	60 (no patients with missing data)	Tx	Prevalent	15.8 (6.2)	57.0	Jewish 57.0 Arab 43.0	CAKUT 42.0 Genetic disorders 20.0	LR (anaemia, dyslipidaemia)

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
	Jerusalem, Israel								Steroid-resistant nephrotic syndrome 25.0 Other 13.0	
Feber et al. (2008)[90]	Single-centre, Canada	Cross-sectional	23 (no patients with missing data)	Tx	Prevalent	8.6 (range 1.6-16.8)	56.0	NR	CAKUT 34.0 FSGS 8.0 Nephronophthisis 9.0 Other 49.0	LR (hypertension, dyslipidaemia)
Chavers et al. (2009)[81]	USRDS, (USA)	Cross-sectional	624 (70)	HD	Prevalent	13.8 (3.8)	56.6	White 48.6 Black 40.1 Other 11.3	CAKUT 34.0 Acquired 50.8 Other 15.2	LR (obesity, hypertension)
Ramirez-Cortes et al. (2009)[79]	Hospital Infantil, Mexico	Cross-sectional	32 (28)	Tx	Prevalent	14.4 (2.6)	50.0	NR	CAKUT 25.0 GN 6.2 Other 9.4 Unknown 59.4	LR (obesity, hypertension, dyslipidaemia)
Paripovic et al. (2010)[91]	Single centre, Serbia	Cross-sectional	41 (14)	Tx	Prevalent	Median 14.5 (IQR 11.1-17.4)	61.0	NR	CAKUT 46.0 Hereditary 34.0 GN 12.0 Other 8.0	LR (hypertension)
Smith et al. (2010)[104]	Centres for Medicare and Medicaid	Cross-sectional	588 (135)	HD	Prevalent	15.8 (6.2)	57.0	White 49.0 Black 40.0 Other 11.0	NR	LR (abnormal mineral metabolism)

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
	cervices, USRDS, the US									
Denburg et al. (2010)[78]	Children`s hospital of Philadelphia, the US	Cohort	141 (42)	Tx	Incident	Median 12.7 (range 2.1-21.8)	62.0	White 74.0 Black 26.0	CAKUT 48.0 FSGS 18.0 GN 16.0 Other 18.0	LR (obesity)
Wilson et al. (2010)[82]	6 centres, the US	Cross-sectional	306 (72)	Tx	Prevalent	12 (5.1)	57.7	White 62.8 Black 27.8 Other 9.4	Glomerular disease 30.8 Other 69.2	LR (obesity)
Kramer et al. (2011)[64]	ESPN/ERA-EDTA (15 European countries)	Cross-sectional	3,337 (448)	HD, PD, Tx	Incident and prevalent	Range 0-17	60.3	NR	CAKUT 42.3 GN 13.5 Cystic kidneys 10.2 Hereditary nephropathy 8.0 Other 26.0	LR (hypertension)
Basiratnia et al. (2011)[92]	Transplant clinic, Shiraz University of medical Sciences, Iran	Cross-sectional	66 (NR)	Tx	Prevalent	17.4 (4.3)	48.0	NR	CAKUT 34.0 Glomerular disease 27.0 Hereditary disease 28.0 Unknown 11.0	LR (hypertension)
Chaudhuri et al. (2011)[85]	Lucile Packard Children`s	Cross-sectional	24 (no patients	HD, PD	Incident and prevalent	14.5 (4.2)	46.0	NR	CAKUT 24.0 Vasculitis 17.0	LR (hypertension)

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
	Hospital, the US		with missing data)						Autoimmune 12.0 FSGS 8.0 Renal cortical necrosis 8.0 Unknown 17.0 Other 14.0	
Sinha et al. (2012)[97]	12 nephrology units in the UK	Cohort	564 (NR)	Tx	Incident	Median 9.0 (IQR 4.5-2.0)	66.7	White 82.1 Other NR	CAKUT 55.5 Other NR	LR (hypertension)
Halbach et al. (2012)[96]	NAPRTCS, (the US, Canada, Mexico and Costa Rica), 150 centres	Cross-sectional	3,437 (no patients with missing data)	HD, PD	Prevalent	Range 1-21	53.1	White 45.1 Black 27.1 Hispanic 20.6 Other 7.2	CAKUT 26.9 Glomerular 44.9 Other 20.8 Missing 7.4	LR (hypertension)
Van Stralen et al. (2012)[42]	ESPN/ERA-EDTA (19 European countries)	Cross-sectional	2,351 (imputed)	HD and PD	Incident and prevalent	Range 0-18	56.4	NR	CAKUT 39.6, GN 17.9 Cystic kidney 10.0 Hereditary nephropathy 7.9 Other/ unknown 24.6	LR (anaemia)

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
Borzych-Duzalka et al. (2013)[22]	IPPN Registry, 2007-2011, (12 European countries, the US, Canada, Turkey, Chile, Korea, Argentina, China, Finland, Singapore, Finland, Macedonia, Nicaragua, Uruguay)	Cohort	1,394 (25)	PD	Incident and prevalent	Median 10.2 (IQR 3.9-14.4)	54.2	NR	CAKUT 46.3 GN 27.6 Vasculitis 9.1 Metabolic disease 2.0 Ischaemia 2.1 Other/unknown 12.9	LR and SR (prevalence of anaemia and its association with all-cause mortality)
Bonthuis et al. (2013)[37]	ESPN/ERA-EDTA (25 European countries)	Cross-sectional	4,474 (NR)	HD, PD, Tx	Incident and prevalent	Range 0-16	59.5	NR	CAKUT 41.3 GN 14.2 Cystic kidneys 10.9 Hereditary nephropathy 8.2 Ischaemic renal failure 2.3 HUS 4.6 Metabolic 3.5 Vasculitis 1.8	LR (obesity)

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
Degi et al. (2014)[80]	Single centre, Budapest, Hungary	Cross-sectional	41 (NR)	Tx	Incident	15.7 (3.5)	68.0	NR	Miscellaneous 5.2 Unknown 8.0 CAKUT 37.0 FSGS 17.0 Nephronophtisis 9.0 Cystic renal disease 12.0 Alport syndrome 7.0 Cystinosis 5.0 Other 13.0	LR (obesity)
Kaidar et al. (2014)[69]	Institute of nephrology of Schneider children`s medical centre of Israel	Cohort	77 (1)	Tx	Prevalent	11.44 (5.4)	67.6	NR	CAKUT 52.0 Cystic kidney disease 5.2 Congenital nephrotic syndrome 7.8 Nephronophthisis 9.0 Metabolic disease 5.2 Other 20.8	LR (anaemia, obesity hypertension, dyslipidaemia, abnormal mineral metabolism)

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
Tainio et al. (2014)[93]	Children`s hospital, Helsinki, Finland	Cohort	210 (NR)	Tx	Prevalent	6.9 (5.5)	63.0	NR	NR	LR (hypertension, dyslipidaemia)
Katsoufis et al. (2014)[86]	Single-centre (not specified), USA	Cross-sectional	17 (13)	HD	Prevalent	16.7 (2.9)	41.0	Black 82.0 Hispanic 18.0	NR	LR (hypertension)
Cameron et. al. (2014)[94]	Single-centre, Sweden	Cross-sectional	68 (NR)	Tx	Incident and prevalent	9.1 (5.3)	57.0	NR	CAKUT 39.0 Hereditary 32.0 GN 16.0 Other 13.0	LR (hypertension)
Gulhan et al. (2014)[89]	Single-centre, Ankara, Turkey	Cross-sectional	29 (3)	Tx	Prevalent	13.9 (2.9)	58.6	NR	CAKUT 48.3 Cystinosis/ amyloidosis 20.7 FSGS 17.2 Unknown 13.8	LR (hypertension)
Bonthuis et al. (2014)[40]	ESPN/ERA-EDTA (19 European countries)	Cross-sectional	976 (NR)	HD, PD, Tx	Incident and prevalent	Range 2-17	58.2	NR	CAKUT 38.1 GN 15.0 Cystic kidneys 12.4 Hereditary nephropathy 13.5	LR (dyslipidaemia)

Author (year)	Data sources (country)	Study design	N(n)	Study population						Studies included in LR and/or SR (CVRF studied)
				Type of RRT	Incident/ Prevalent RRT patients	Age in years (SD)*	Male %	Race/ ethnicity %	PRD distribution %	
Bonthuis et al. (2015)[105]	ESPN/ERA-EDTA (9 European countries)	Cross-sectional	1,237 (NR)	Tx	Incident and prevalent	Range 0-18	59.9	NR	Ischemic renal failure 2.0 HUS 3.6 Other 11.1 Missing 4.3 CAKUT 44.4 GN 9.2 Cystic kidneys 10.4 Hereditary nephropathy 14.7 Ischemic renal failure 2.1 HUS 2.9 Other 10.6 Missing 5.7	LR (abnormal mineral metabolism)
Kari et al. (2015)[111]	King Abdulaziz University Hospital, Saudi Arabia	Cohort	1000/(no patients with missing data)	CKD stage 1-5.	Prevalent	4.9 (4.3)	60.8	Saudi 53.9 Other NR	CAKUT 53.7 GN 35.3 Other NR	SR (association of hypertension with all-cause mortality)

N-total number of patients in the study after exclusion of patients with missing data, (n)- excluded patients with missing data, RRT- renal replacement therapy; PRD-primary renal disease; HD-haemodialysis, PD-peritoneal dialysis; Tx-transplanted; GN-glomerulonephritis; CAKUT-congenital anomalies of kidney and urinary tract; HUS- haemolytic uraemic syndrome; FSGS-focal segmental glomerulosclerosis; EPO-erythropoietin; Hb-haemoglobin; Ht-haemotocrit; BMI-body mass index; SBP-systolic blood pressure, DBP- diastolic blood pressure, BP-blood pressure; eGFR-estimated glomerular filtration rate; IQR-Interquartile range. *All age values are means +/- SD, unless otherwise specified. LR-literature review, SR-systematic review. NR-not reported. Number is superscript refers to the study identifier

2.3.1 Part 1. The prevalence of cardiovascular risk factors in patients who initiated RRT in childhood. Literature review

This literature review presents results of the prevalence and patterns of CVRFs in patients who initiated RRT in childhood. According to the ESPN/ERA-EDTA registry, the prevalence of CVRFs significantly differs by treatment modality (dialysis and kidney transplantation) (37, 63, 64). Therefore, it was decided, where possible, to stratify the reported prevalence of CVRFs by treatment modality.

2.3.1.1 Prevalence of anaemia in patients who initiated RRT in childhood

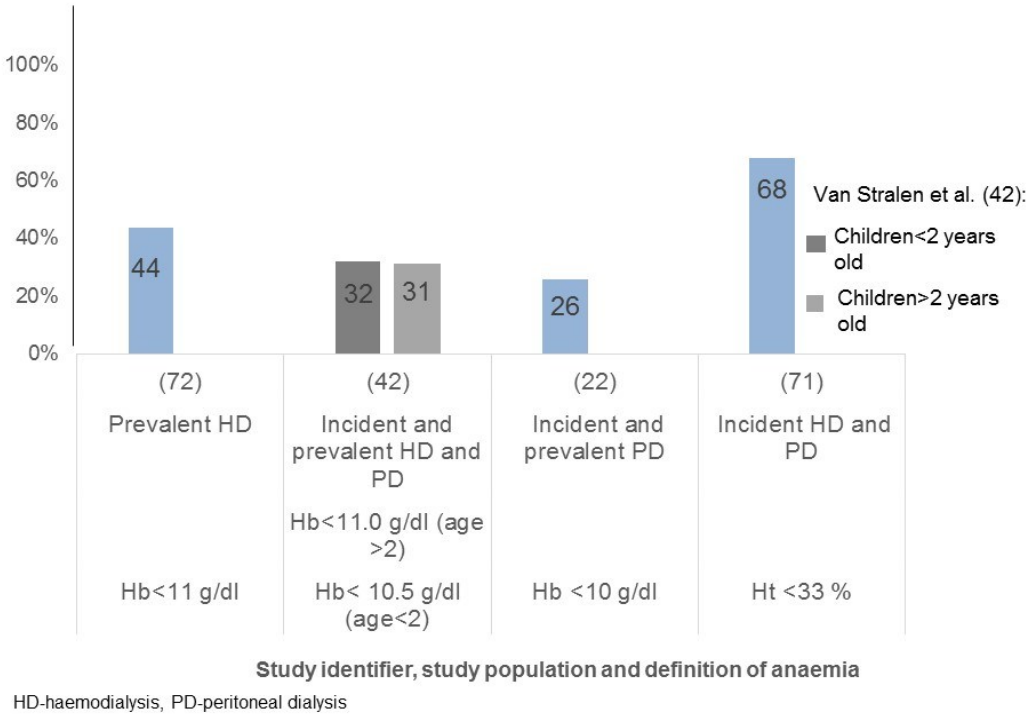
Ten studies[3] reported the prevalence of anaemia. Six were single-centre studies conducted in the USA (65-67), Israel (68, 69) and Australia (70). Four studies were from large international and national renal registries, such as the NAPRTCS (71), the USRDS (72), the ESPN/ERA-EDTA (42) and the IPPN Registries (22).

The sample size of the studies ranged from 50 to 2,351 patients. The mean age of the patients in the included studies ranged from 10.2 to 16 years. The definition of anaemia differed across studies. Five out of ten studies used a single cut-off value for Hb to define anaemia (Hb<11g/dl or <10 g/dl) (22, 66, 67, 69, 72), while three studies used age-dependent cut-off values for Hb (42, 68, 70) and two studies used Ht values (Ht >2SD below published means for age or Ht <33 %) (65, 71). The use of erythropoietin (EPO) was included in the definition of anaemia in three studies (65, 68, 69).

[3] Six cohort and four cross-sectional studies

The prevalence of anaemia among dialysis populations was reported by four multi-centre studies conducted by the USRDS (72), the IPPN (22), the ESPN/ERA-EDTA (42), and the NAPRTCS (71) registries, and ranged from 26-68% (Figure 4).

Figure 4. Prevalence of anaemia in studies that included a dialysis population. The number within the bars refers to the proportion of patients with anaemia; the number in parentheses refers to the reference number of the study



Study reference	(72)	(42)	(22)	(71)
Sample size	677	2,351	1,394	1,942
95% CI	40-47	30-34	24-28	66-70
		29-33		

CI-confidence interval around reported proportion of patients with anaemia presented in Figure 4. The order of multiple CIs in the table within the study correspond to the proportions presented in the figure in order from left to right.

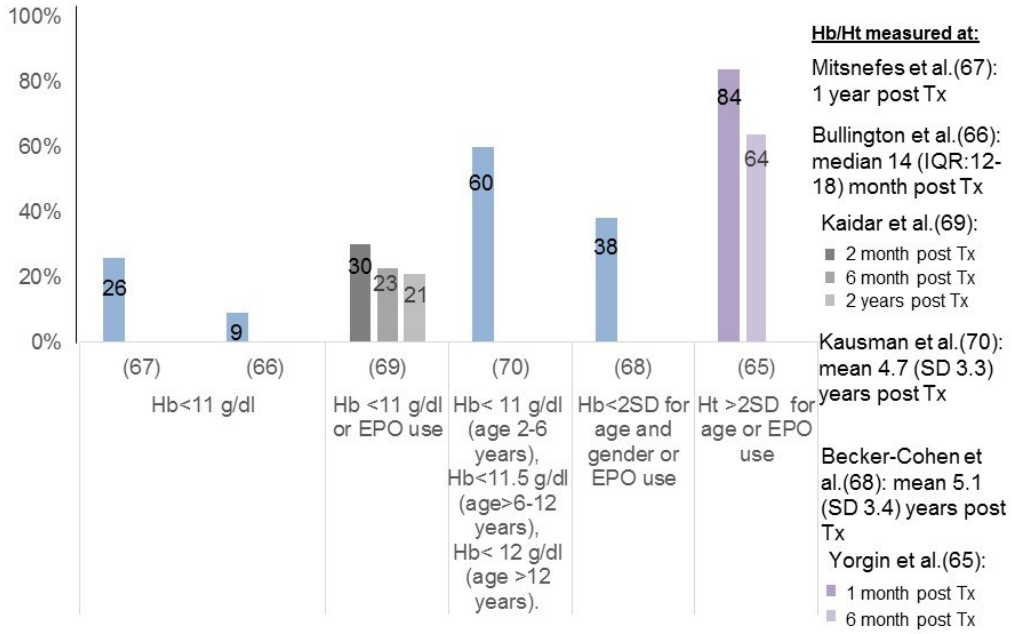
The NAPRTCS (71) registry reported the highest prevalence of anaemia compared to other studies. In part, this may be explained by the use of Ht to define anaemia in this study, whilst other studies used Hb. As patients` fluid status influences Ht more than Hb (73), it is likely that the NAPRTCS study reported higher prevalence of anaemia due to low Ht values as a result of patients being hypervolemic.

Among three studies that used Hb to define anaemia the USRDS registry reported the highest prevalence (72), while the IPPN registry showed the lowest (22). The difference between the two studies may be explained by the variation in treatment practices and different cut-off values of Hb. The USRDS study (72) used higher cut-off values of Hb that may partly explain the higher prevalence of anaemia in this study compared to the IPPN study (22). The USRDS registry study (72) included HD patients, while the IPPN study included PD patients (22). Volume overload is more common among HD patients compared to PD patients (74). As Hb/Ht values are affected by patients fluid status and hypervolaemic patients may have lower Hb/Ht values (73) the USRDS study might have been expected to report a higher prevalence of anaemia compared to the IPPN study.

The ESPN/ERA-EDTA study (42) reported the overall prevalence of anaemia among both HD and PD patients stratified by age, since the authors used age-dependent cut-off Hb values. This study also showed that mean Hb values were higher in PD patients compared to HD patients.

The prevalence of anaemia remains high after transplantation. The overall prevalence of anaemia in transplanted patients was reported by six single-centre studies widely ranging from 9-84% (Figure 5).

Figure 5. Prevalence of anaemia in studies that included a transplanted population. The number within the bars refers to the proportion of patients with anaemia; the number in parentheses refers to the reference number of the study



Hb-haemoglobin, Ht-haematocrit, Tx-transplantation, SD-standard deviation, IQR-interquartile range, EPO-erythropoetin

Study reference	(67)	(66)	(69)	(70)	(68)	(65)
Sample size	301	47	77	50	60	162
95% CI	21-31	0.8-17	18-40 14-32 12-30	37-63	26-50	78-89 57-71

CI-confidence interval around reported proportion of patients with anaemia presented in Figure 5. The order of multiple CIs in the table within the study correspond to the proportions presented in the figure in order from left to right.

The highest prevalence was reported by single hospital study from the US which used Ht values to define anaemia (65), while other studies used Hb. The explanation of a higher prevalence of anaemia in studies that used Ht compared to Hb is given in the section above. Different inclusion criteria for study populations may also have contributed to the variation of the prevalence in transplanted patients. For example, a study from a single-hospital in the US (66) might have included healthier transplanted patients. This could be because the latter study included patients without structural cardiac anomalies and a functioning graft for at least one year with an eGFR >40 mL/min/1.73 m^2. Therefore, selective inclusion of healthier patients may explain the fact that the authors reported a lower prevalence of anaemia compared to other studies.

Another possible explanation for the variation in reported prevalence among transplanted and dialysis patients might be the use of different laboratory methods for Hb/Ht measurements in various centres. However, the information about the methods for Hb/Ht measurements is not provided within the articles and as a result it is not possible to identify the potential for misclassification of anaemic/non-anaemic patients. It is likely that the majority of centres used the Hb cyanide method for determination of Hb in blood, as it is a gold standard reference method (75). It is worth noting that other methods, such as automated haematology analyser may have also been used. When compared to the reference method, automated haematology analyser methods showed a tendency to deviate towards higher Hb values (75, 76). If some of the studies used the latter method, they might have reported a lower prevalence compared to the studies that used the reference method. For multi-centre and registry studies it is possible that a mixture of Hb measuring methods was used and ideally standardisation would be required to be applied ensure data are comparable.

Other factors may have contributed to differences in reported prevalence of anaemia between studies. According to the ESPN/ERA-EDTA registry low ferritin and albumin levels and high PTH levels are associated with lower levels of Hb (42). Information on the prevalence of these risk factors was not provided in all studies, therefore, it was not possible to assess the effect of ferritin, albumin and PTH on the difference in reported prevalence of anaemia across the studies. Studies that may have included a population of patients with low ferritin, albumin, or high PTH levels, could have reported a higher prevalence of anaemia.

2.3.1.2 Prevalence of obesity in patients who initiated RRT in childhood

Nine[4] studies reported the prevalence of obesity including five single-centre and four multi-centre studies. Single-centre studies were from the USA (77, 78), Mexico (79), Israel (69) and Hungary (80). Four multi-centre studies reported results from national and international renal registries, and included the NAPRTCS (54), the USRDS (81), the ESPN/ERA-EDTA (37), and a multi-centre study in the USA involving six centres (82).

The sample size of the studies ranged from 32 to 6,658 patients. The mean age ranged from 4.3 to 15.7 years. Seven studies defined obesity as BMI $\geq 95^{th}$ percentile for age, sex and race (54, 77-82), while in two studies obesity was defined as BMI SD scores (SDS) >+3 (37) or BMI > 30 kg/m^2 (69). Six studies used normative reference data for

[4] Five cross-sectional and four cohort studies

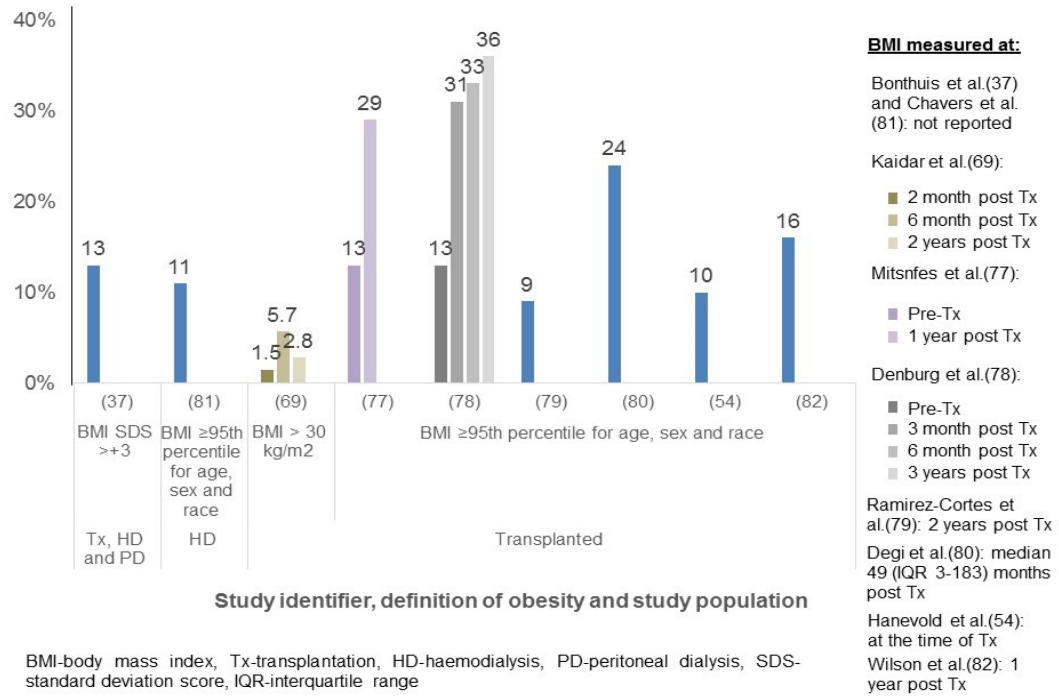
BMI obtained from the age and sex matched general US population, while information about reference centile BMI charts was missing in three studies (79, 80, 82).

The prevalence of obesity stratified by RRT population and definition of obesity is presented in Figure 6. The overall prevalence of obesity among HD, PD and transplanted patients was reported by one study performed by the ESPN/ERA-EDTA registry (37). Although the ESPN/ERA-EDTA study did not report stratified prevalence by RRT modality, the authors stated that the prevalence of obesity was higher among transplanted population than among dialysis population (37). Only one study reported the prevalence of obesity in a dialysis population (81), whilst the remaining studies included patients after kidney transplantation.

The prevalence of obesity in transplanted patients ranged from 1.5% to 36% across studies. The wide variation of the prevalence may be partly explained by the different definitions of obesity used in the studies. A single-centre study from Israel (69) reported the lowest prevalence of obesity compared to other studies. This is the only study that applied the definition used for adults to define obesity in a paediatric population. Other studies used age, sex and race dependent percentiles of the general population. In children, BMI is dependent on age and sex and it is, therefore, recommended that obesity is defined according to the age and sex dependent reference percentiles. The application of adult criteria to define obesity in a paediatric population is likely to under-estimate the prevalence of obesity in children.

Increasing prevalence of obesity after kidney transplantation was shown by two studies (77, 78). Both of these showed that the pre-transplant prevalence of obesity was lower compared to the post-transplant prevalence.

Figure 6. Prevalence of obesity in studies that included dialysis and transplanted populations. The number within the bars refers to the proportion of patients with obesity; the number in parentheses refers to the reference number of the study



BMI-body mass index, Tx-transplantation, HD-haemodialysis, PD-peritoneal dialysis, SDS-standard deviation score, IQR-interquartile range

Study ref.	(37)	(81)	(69)	(77)	(78)	(79)	(80)	(54)	(82)
Sample size	4,474	624	77	50	141	32	41	6,658	306
95% CI	12-14	8.5-13	0-4.2 0.5-10 0-6.5	3.6-22 16-41	7.4-18 23-38 25-41 28-44	0-18	11-37	9-11	12-20

Ref-reference, CI-confidence interval around reported proportion of patients with obesity presented in Figure 6. The order of multiple CIs in the table within the study correspond to the proportions presented in the figure in order from left to right.

One of the possible reasons for post-transplant weight gain may be glucocorticoid therapy, which is an immunosuppressive therapy and is initiated after kidney transplantation to prevent a graft failure. Glucocorticoids appear to promote the differentiation of adipocytes precursor cells into mature fat cells resulting in abdominal obesity (83).

Differences in age distribution between studies might have contributed to the variation of the prevalence of obesity reported in transplanted patients. Younger patients receiving RRT usually have lower prevalence of obesity compared to older patients (37). The NAPRTCS (54) reported a prevalence of 10%, which was lower than the 13% reported in the other two single-centre studies (77, 78). The lower prevalence reported by the NAPRTCS may in part be explained by the study population being younger (mean age 4.3 years old) than in the other two studies (mean 13.5 years (SD5.3) and median 12.7 years (IQR 2.1-21.8)).

Moreover, different lengths of follow-up since kidney transplantation across studies may have contributed to differences in prevalence of obesity, since longer time after kidney transplantation is associated with greater increase in BMI (37). For example, Denburg et al. (78) reported that the prevalence of obesity post-transplantation increased from 31% at three months to 33% at six months and 36% at three years.

Additionally, children receiving RRT experience a growth retardation, which is influenced by nutritional and metabolic alterations. According to the ESPN/ERA-EDRA registry, transplanted children with severe and moderate growth retardation (height SDS<-3; height SDS between -3 and -1.88 SDS, respectively) have an

increased risk of being overweight compared to children with less growth retardation (height SDS of ≥-1.88) (37). However, information on patients' stature was not reported in all studies, therefore, it was not possible to assess the effect of this factor on variation in obesity prevalence across studies. Studies that may have included patients with severe or moderate growth restrictions could have pointed to a higher prevalence of obesity.

2.3.1.3 Prevalence of hypertension in patients who initiated RRT in childhood

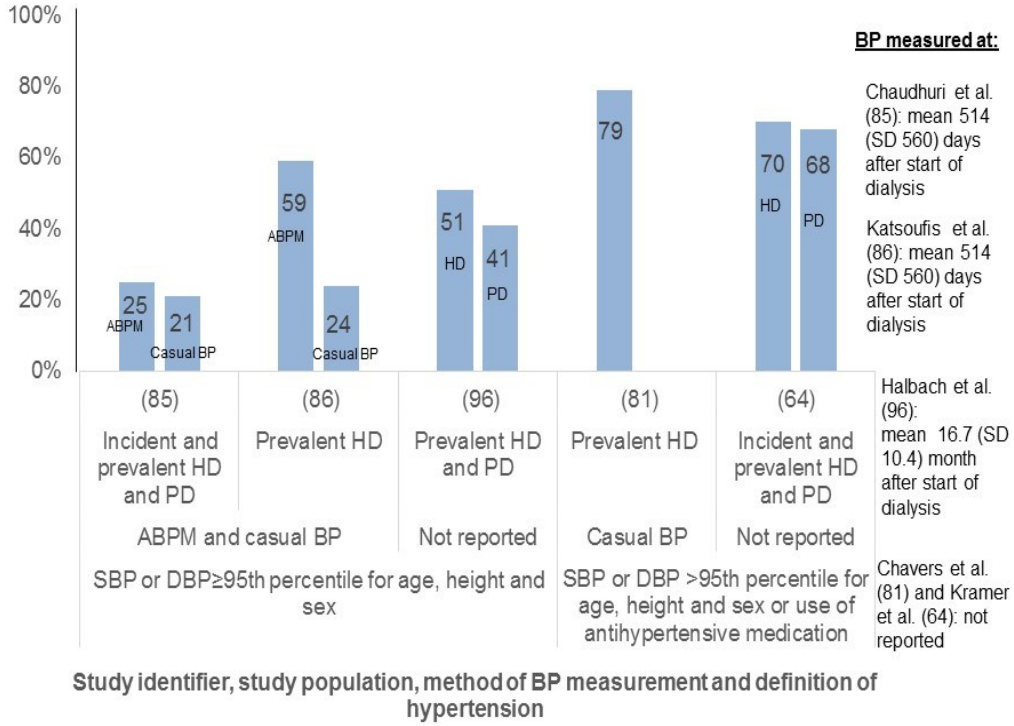
Nineteen[5] studies described the prevalence of hypertension. Fourteen studies were single-centre studies and five were multi-centre studies. Single-centre studies were from the USA (66, 84-86), Austria (87), Turkey (88, 89), Canada (90), Mexico (79), Serbia (91), Iran (92), Israel (69), Finland (93) and Sweden (94). Multi-centre studies were from large national and international renal registries and included the NAPRTCS registry (95, 96), the USRDS registry (81), the ESPN/ERA-EDTA registry (64) and a multi-centre study from 12 nephrology units in the UK was included (97).

The sample size of the studies ranged from 17 to 3,337 patients. The mean age ranged from 6.9 to 17.4 years at data collection. Included studies were heterogeneous by methods of BP measurements and definition of hypertension. Seven studies used casual BP, using mostly oscillometric or sphygmomanometer methods (66, 69, 81, 84, 90, 93, 98), two studies used ambulatory blood pressure monitoring (ABPM) (87, 94) while the other five studies measured both casual BP and ABPM (85, 86, 89, 91, 92). Information on the methods of BP measurement was not given in five studies (64, 79,

[5] Four cohort and fifteen cross-sectional

88, 95, 96). To define hypertension 14 studies used measured BP above the 95th percentile for age, height and sex of the general US population. Five studies defined hypertension based on a combination of BP measurement above the 95th percentile for age, height and sex or use of antihypertensive medication. The prevalence of hypertension among dialysis populations stratified by method of BP measurement and definition of hypertension is summarised in Figure 7. Prevalence of hypertension ranged widely across studies from 21% to 79%.

Figure 7. Prevalence of hypertension in studies that included a dialysis population. The number within the bars refers to the proportion of patients with hypertension; the number in parentheses refers to the reference number of the study



HD-haemodialysis, PD-peritoneal dialysis, SD-standard deviation, BP-blood pressure, SBP-systolic BP, DBP-diastolic BP, ABPM-ambulatory blood pressure monitoring

Study reference	(85)	(86)	(96)	(81)	(64)
Sample size	24	17	3,437	50	3,337
95% CI	7.6-42	35-82	49-53	68-90	68-72
	5-37	3.6-44	39-42		66-70

CI-confidence interval around reported proportion of patients with hypertension presented in Figure 7. The order of multiple CIs in the table within the study correspond to the proportions presented in the figure in order from left to right.

Two studies that used both casual and ABPM methods to measure BP in their study population showed that the prevalence of hypertension was lower when measured by casual BP compared to the ABPM method (85, 86). This could be partly explained by the fact that ABPM method reveals nocturnal hypertension, since BP is measured during 24 or 48 hours (86).

Among five studies of dialysis patients (64, 81, 85, 86, 96), prevalence of hypertension was highest in the studies reported by the USRDS registry (81) and the ESPN/ERA-EDTA registry (64) . The high prevalence may be partly explained by the definition of hypertension that these studies used. Both studies defined hypertension as BP levels>95th percentile for age, gender and height or use of antihypertensive medication. Inclusion of antihypertensive medication in the definition leads to an increase in prevalence of hypertension compared to the use of BP alone because in this case patients with controlled BP are classified as hypertensive patients. Moreover, some antihypertensive medication (specifically angiotensin-converting-enzyme inhibitors) might, in some cases, be prescribed irrespective of BP levels for their nephroprotective effect (97). Therefore, their inclusion in the definition might over-estimate prevalence of hypertension.

Another possible explanation for the difference in the reported prevalence might be the difference in timing of BP measurements relative to the dialysis procedure. Due to the volume overload, pre-dialysis BP readings tend to be higher compared to post-dialysis. Therefore, studies that measured BP before dialysis might have overestimated the prevalence of hypertension compared to the studies that measured BP after the dialysis procedure. However, the timing of the BP measurement relative to dialysis therapy was rarely reported, therefore, it was not possible to compare the prevalence

of hypertension by timing of BP readings. Only two studies mention this: the USRDS registry (81) and the ESPN/ERA-EDTA registry (64). The USRDS registry (81) used mean of the pre- and post-dialysis BP measurements for their analysis. The authors have reported that 8% of patients would be re-categorised from hypertensive pre-dialysis to normotensive post-dialysis. The ESPN/ERA-EDTA registry (64) stated that the registry usually requests pre-dialysis BP measurements; for this reason, this study might have overestimated the prevalence of hypertension in the dialysis population.

Table 5 shows the prevalence of hypertension among transplanted populations stratified by method of BP measurement and definition of hypertension. The overall prevalence ranged from 18% to 87%. Three studies measured both casual BP and ABPM (89, 91, 92). All three studies showed a lower prevalence of hypertension measured by casual BP compared to ABPM method. There was no clear difference in prevalence of hypertension between studies that used exclusively casual BP versus those studies that used exclusively ABPM and between combined definition of BP levels with medication versus the use of BP alone.

The information on BP measurement method was missing in five studies: two studies from the NAPRCS (95, 96); one the ESPN-ERA-EDTA (64) and two single-centre studies (79, 88). It is likely that in the multi-centre studies a mixture of ABPM and casual BP measurement methods was used. Since the authors did not report on methods of BP measurement, it is not possible to examine the potential for misclassification of hypertensive/non-hypertensive patients.

In addition to variation in definition of hypertension and method of BP measurement, duration of RRT could contribute to the heterogeneity in hypertension prevalence

between studies. Different studies measured the prevalence of hypertension in population of patients with different duration of RRT. According to the ESPN/ERA-EDTA, shorter duration of RRT is associated with a higher risk of hypertension (64). Therefore, studies that may have included populations with shorter duration of RRT might have reported a higher prevalence of hypertension. The information on overall duration of RRT, including time on dialysis before transplantation was not reported in the majority of the studies, as a result, it was not possible to compare the prevalence of hypertension based on the duration of RRT.

Table 5. Method of BP measurement, definition and prevalence of hypertension in transplanted population

Method of BP measurement	Definition of hypertension	Author (year)	Sample size	Prevalence of hypertension % (95% CI)		Time of BP measurement post transplantation
ABPM and casual BP	SBP or DBP>95th percentile for age, height and sex	Gulhan et al. (2014)[89]	29	76 (60-91) by ABPM	21 (5.8-35) by casual BP	mean 24.6 (SD 22.2) months
		Paripovic et al. (2010)[91]	41	68 (54-82) by ABPM	42 (27-57) by casual BP	median 2.5 (IQR 0.8 to 4.6) years
	SBP or DBP ≥95th percentile for age, height and sex or use of antihypertensive medication	Basiratnia et al. (2011)[92]	66	76 (65-86) by ABPM	57 (45-69) by causal BP	6 months
Casual BP	SBP>2 SD above the mean	Feber et al. (2008)[90]	23	69 (51-88)		mean 116 (SD16) days
				87 (73-100)		mean 3.35 (SD 2.8) years
	SBP or DBP>95th percentile for age, sex and height	Bullington et al. (2006)[66]	47	43 (29-57)		median 14 (IQR 12–18) months
		Mitsnefes et al. (2003)[84]	159	62 (54-70)		1 year
		Sinha et al. (2012)[97]	564	27 (24-31)		6 months
				27 (24-31)		1 year
				26 (22-30)		2 years
				26 (23-29)		5 years
	>2SD for age, sex and height or use of antihypertensive medication	Kaidar et al. (2014)[69]	77	52 (41-63)		2 months
				28 (18-37)		6 months
				22 (12-31)		2 years
	SBP or DBP ≥95th percentile for age, height and sex or use of antihypertensive medication	Tainio et al. (2014)[93]	210	87 (82-91)		1.5 years
				62 (55-69)		5 years
ABPM	Mean day-time or night-time SBP or DBP>95th percentile for age, height and sex	Cameron et. al. (2014)[94]	68	65 (54-76)		1 year
		Kitzmueller et al. (2004)[87]	39	58 (43-73)		3 months

Method of BP measurement	Definition of hypertension	Author (year)	Sample size	Prevalence of hypertension % (95% CI)	Time of BP measurement post transplantation
Not reported	SBP or DBP ≥95th percentile for age, height and sex	Ramirez-Cortes et al. (2009)[79]	32	53 (36-70)	2 years
		Baluarte et al. (1994)[95]	277	40 (34-46)	1 month
				29 (24-34)	6 months
				26 (21-31)	12 months
				18 (13-23)	24 months
	Not reported	Mir et al. (2005)[88]	72	38 (26-49)	3 months
				53 (42-65)	1 year
	SBP or DBP ≥95th percentile for age, height and sex or use of antihypertensive medication	Kramer et al. (2011)[64]	3,337	67 (65-68)	not reported

BP- blood pressure, ABPM-ambulatory BP monitoring, SBP-systolic BP, DBP-diastolic BP, SD-standard deviation, IQR-interquartile range. Number is superscript refers to the study identifier; CI-confidence interval

2.3.1.4 Prevalence of dyslipidaemia in patients who initiated RRT in childhood

Nine[6] studies described the prevalence of dyslipidaemia in patients who initiated RRT in childhood. Almost all studies were from a single centre with only one multi-centre study performed by ESPN/ERA-EDTA registry (40). Single-centre studies were from the USA (99, 100), Turkey (88), Israel (68, 69) Canada (90), Finland (93) and Mexico (79).

The sample size of studies ranged from 23 to 210 patients. The mean age ranged from 6.9 to 15.8 years. Eight studies included a transplanted population and one study included both dialysis and transplanted patients. One study did not report the definition of dyslipidaemia (88). Cut-off values for lipid levels showed a variation among the studies that reported the definition of dyslipidaemia. Cut-off levels for hypercholesterolemia ranged from 170 to 200 mg/dl (4.4 to 5.2 mmol/l). Cut-off levels for hypertriglyceridemia ranged from 100 to 200 mg/dl (1.1 to 2.3 mmol/l). Cut-off levels for low high-density lipoprotein (HDL) ranged from 35 to 40 mg/dl (0.9 to 1.0 mmol/l), while cut-off levels for high low-density lipoprotein (LDL) ranged from 100 to 145 mg/dl (2.6 to 3.7 mmol/l). Only one study included the use of cholesterol lowering medication in the definition of dyslipidaemia (90).

Table 6 summarises the definition and prevalence of hypercholesterolemia and abnormal lipids fractions. The prevalence of hypercholesterolemia among transplanted patients ranged from 15 to 58%. When stratified by definition of hypercholesterolemia, studies that used lower cut-off cholesterol levels do not report higher prevalence of

[6] five cross-sectional and five cohort studies

hypercholesterolemia than those that used higher cut-off points. The overall prevalence of low HDL-cholesterol, high non-HDL cholesterol and hypertriglyceridemia ranged from 5% to 18.7% (40, 68, 79, 93), 10% to 31% (40, 68, 93) and 8% to 54% (40, 68, 69, 79, 88, 93, 99, 100), respectively. As with hypercholesterolemia, there is no clear trend that the studies that used lower cut-off levels report a higher prevalence.

Possible explanations for the variation of the prevalence across studies may be different populations. For instance, among three studies that used the same threshold of > 200 mg/dl (68, 99, 100) two US studies (99, 100) reported a higher prevalence compared to the study from Israel (68). This might be explained by the fact that the general paediatric population in the US has the highest prevalence of obesity compared to the European population. A cross-sectional survey on adolescents from the general population of 13 European countries, Israel and the US showed that the highest prevalence of overweight/obesity was found in the US (101).

Table 6. Definition and prevalence of dyslipidaemia in patients who initiated RRT in childhood

RRT population	Author (year)	Sample size	Prevalence of high total cholesterol % (95% CI)	Prevalence of high non-HDL-cholesterol % (95% CI)	Prevalence of low HDL- cholesterol % (95% CI)	Prevalence of high TG % (95% CI)	Time of lipids measurements
Transplanted	Silverstein et el. (2000)[99]	62	52 (39-64)	NR	NR	52 (39-64)	mean 6.7 years (SD 3.1) post Tx
	Chavers et al. (2003)[100]	59	34 (22-46)	NR	NR	54 (41-67)	pre-Tx
			46 (33-59)			36 (24-48)	1 year post Tx
			58 (45-70)			29 (17-41)	3 year post Tx
			41 (28-54)			14 (5.1-23)	5 years post Tx
	Becker-Cohen et al. (2006)[68]	60	15 (5.9-24)	10 (2.4-18)	15 (5.9-24)	8 (1.1-14)	mean 5.1 (SD 3.4) years post Tx
	Kaidar et al. (2014)[69]	77	49 (38-60)	NR	NR	50 (39-61)	2 months post Tx
			40 (29-50)			47 (36-58)	6 months post Tx
			22 (13-31)			12 (4.7-19)	2 years post Tx
	Feber et al. (2008)[90]	23	44 (24-64)	NR	NR	NR	mean time of 116 (SD 16) days
			47 (27-67)				mean time of 3.35 (SD 2.8) years post Tx
	Ramirez-Cortes et al. (2009)[79]	32	25 (10-40)	NR	19 (5.2-32)	38 (21-54)	2 years post Tx
	Tainio et al. (2014)[93]	210	39 (32-46)	31 (25-37)	8 (4.3-12)	34 (28-40)	1 year post Tx
			31 (25-37)	24 (18-30)	5 (2.1-7.9)	28 (22-34)	5 years post Tx
	Mir et al. (2005)[88]	72	40 (29-52)	NR	NR	9.7 (2.8-17)	NR

RRT population	Author (year)	Sample size	Prevalence of high total cholesterol % (95% CI)	Prevalence of high non-HDL-cholesterol % (95% CI)	Prevalence of low HDL- cholesterol % (95% CI)	Prevalence of high TG % (95% CI)	Time of lipids measurements
Transplanted HD and PD	Bonthuis et al. (2014)[40]	976	NR	55 (51-58) PD	24 (21-26) PD	74 (71-77) PD	NR
				24 (21-28) HD	38 (35-41) HD	61 (57-64) HD	
				23 (20-25) Tx	13 (11-15) Tx	45 (42-48) Tx	

HD-haemodialysis, PD-peritoneal dialysis; Tx-transplantation; TG-triglycerides; HDL-cholesterol-high density lipoprotein cholesterol; SD-standard deviation, NR-not reported. Number is superscript refers to the study identifier; CI-confidence interval

Total cholesterol >200 mg/dl

Total cholesterol >180 mg/dl

Total cholesterol >170 mg/dl

Definition of hypercholesterolemia not reported

Non-HDL cholesterol >145 mg/dl

Non-HDL cholesterol >130 mg/dl

Definition of high non-HDL cholesterol not reported

HDL cholesterol <40 mg/dl

HDL cholesterol <10th percentile for age and sex

Definition of low HDL cholesterol not reported

TG>200 mg/dl

TG>150 mg/dl

TG>140 mg/dl

TG>100 mg/dl

TG≥90th percentile for age and sex

Definition of hypertriglyceridemia not reported

Given that the high BMI is associated with a less favourable lipid profile (40) the US studies may have reported a higher prevalence of dyslipidaemia. Unfortunately, information on mean BMI was not provided by the authors, therefore, it was not possible to compare their results by BMI level.

Different definitions of dyslipidaemia could also in part explain the difference in the reported prevalence. For example, two studies from Canada (90) and Mexico (79) used simillar cut-off values of >170 mg/dl, however, the Canadian study reported a higher prevalence compared to the Mexican study. This is in part because Canadian study (90) included the use of cholesterol lowering medication in the definition of dyslipidaemia. In this case, patients with controlled lipids levels may have been classified as dyslipidaemic. Two studies from Turkey (88) and Finland (93) did not report the cut-off levels for the definition of hypercholesterolemia, therefore, it was not possible to compare their estimates with other studies.

The variation of the prevalence of hypercholesterolemia across studies might be additionally explained by pre-transplant hypercholesterolemia. Pre-transplant hypercholesterolemia is associated with increased cholesterol levels post-kidney transplantation (82). However, the information on the pre-transplant hypercholesterolemia was not available in all studies, therefore, it was not possible to assess the effect of this factor on the difference in prevalence of hypercholesterolemia across studies.

Only one study compared the prevalence of lipid fractions by type of RRT (40). Using data from the ESPN/ERA-EDTA registry this study showed that the prevalence of high non-HDL cholesterol, low HDL-cholesterol and hypertriglyceridemia was higher

among dialysis patients compared to transplanted patients (40). Specifically, patients receiving PD had a higher prevalence of high non-HDL cholesterol and hypertriglyceridemia compared to HD and transplanted patients. The high glucose load from the dialysis fluid may explain the higher prevalence of dyslipidaemia among PD patients. Previous research has shown a correlation between serum lipids and intraperitoneal glucose absorption (102).

The variation of the prevalence of lipid fractions across all studies might be additionally explained by the use of medication. Thiazide diuretics and beta-adrenergic blockers, that are used to reduce a high BP, have been shown to raise serum lipids levels (82). However, medication use was also not reported in all studies and, therefore it was not possible to assess the effect of medication on the prevalence of dyslipidaemia in the studies.

Moreover, information on the method of lipids measurements was not reported in all studies. It is expected that the majority of studies have measured lipids following an overnight fast, as it is a common and accurate method (103). However, if lipids were measured under non-fasting conditions there may be an underestimation of the real prevalence of HDL-cholesterol, as the levels of non-fasting HDL-cholesterol tend to be lower compared to the measurements taken post an overnight fast (103). By contrast, the prevalence of hypertriglyceridemia might be overestimated if measured in non-fasting conditions as the level of non-fasting triglycerides increases compared to the fasting state (103).

2.3.1.5 Prevalence of abnormal mineral metabolism in patients who initiated RRT in childhood

Since the literature search strategy did not include specific search terms for abnormal mineral metabolism, it is probable that not all relevant papers were identified. As a result, the studies that were incidentally identified, and which are summarised below, are a selected group. Three studies were identified and included (69, 104, 105). Two studies were from large national registries, the USRDS (104) and the ESPN/ERA-EDTA registry (105), while one study was a single-centre study (69). The sample sizes were 77 (69), 588 (104) and 1,237 (105). Two studies reported the mean (SD) age, which was 15.8 (104) years and 11.4 (69) years, while another study reported the age range (0-18 years) (105). Studies were heterogeneous in terms of RRT population. The ESPN/ERA-EDTA registry and the single-centre study included patients post-kidney transplantation (69, 105), while the study conducted by the USRDS registry included HD patients (104).

The ESPN/ERA-EDTA registry (105) used GFR dependent cut–off values for PTH and age dependent for serum Ca and P (Table 7). Single-centre study from Israel only reported high PTH levels, defined as PTH> 108 pg/ml (69). The USRDS registry also reported only abnormal PTH levels and did not provide the definition of this (104).

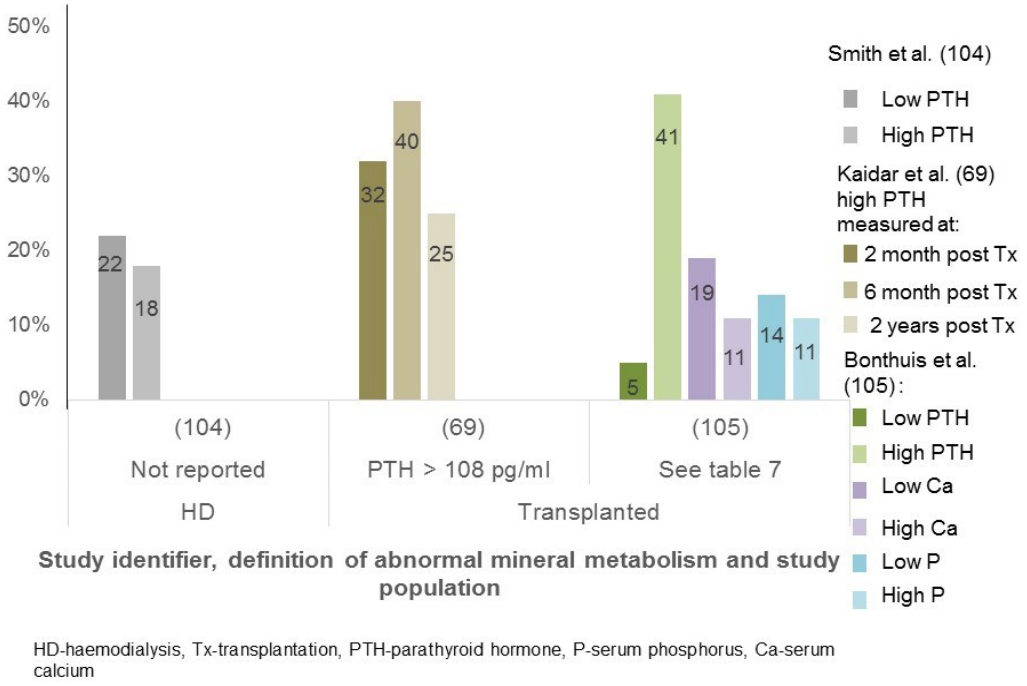
Table 7. Definition of abnormal mineral metabolism reported in the ESPN/ERA-EDTA study (105)

PTH (pg/ml)	**Target level**		**Target level Ca (mg/dl)**	**Target level P (mg/dl)**
GFR (ml/min per 1.73 m^2)		Age (year)		
>59	10-65	0-2	8.8-11.3	4.8-7.4
29<GFR≤59	10-65	3-5	9.4-10.8	4.5-6.5
15 ≤ GFR≤29	130-195	6-12	9.4-10.3	3.6-5.8
<15	130-195	13-18	8.8-10.2	2.3-4.5

PTH-parathyroid hormone, Ca-serum calcium, P/serum phosphorus

Figure 8 presents the prevalence of abnormal mineral metabolism stratified by type of RRT. The prevalence of high PTH levels in transplanted patients was 25% (69) and 41% (105) in the study from Israel and the ESPN/ERA-EDTA study, respectively. Varying duration post kidney transplantation at the time of the study may contribute to the variation of the reported prevalence as longer time post kidney transplantation is associated with lower risk of high PTH levels (105). However, it was not possible to compare the results of the two studies as the ESPN/ERA-EDTA (105) did not report the duration of time post kidney transplantation at the time of the study. The prevalence of high PTH level in the study from Israel (69) was reported at two months, six months and two years post kidney transplantation with the lowest prevalence reported at the last follow-up time.

Figure 8. Prevalence of abnormal mineral metabolism in dialysis and transplanted populations. The number within the bars refers to the proportion of patients with abnormal mineral metabolism; the number in parentheses refers to the reference number of the study



HD-haemodialysis, Tx-transplantation, PTH-parathyroid hormone, P-serum phosphorus, Ca-serum calcium

Study reference	(104)	(69)	(105)
Sample size	588	77	1,237
95% CI	19-25	22-42	3.7-6.2; 38-44
	15-21	29-51	17-21; 9.2-12
		15-35	12-16; 9.2-12

CI-confidence interval around reported proportion of patients with abnormal mineral metabolism presented in Figure 8. The order of multiple CIs in the table within the study correspond to the proportions presented in the figure in order from left to right.

Serum Ca and P levels were reported in one study conducted by the ESPN/ERA-EDTA (105). Abnormal serum P levels were observed in 25% (14% hypophosphatemia and 11% hyperphosphatemia) and altered serum Ca in 30% (19% hypocalcaemia, 11% hypercalcemia) of transplanted patients. The authors have stated that female sex, pre-emptive transplantation and longer time since transplantation are associated with lower risk of having mineral levels above the target range.

2.3.1.6 Prevalence of metabolic syndrome in patients initiated RRT in childhood

Three studies (79, 82, 93) described prevalence of multiple CVRFs in patients post-kidney transplantation. All three studies described the prevalence of metabolic syndrome (MeS). This was defined as present if children had at least three of the following five risk factors: overweight, hypertension, low HDL-cholesterol, elevated triglycerides or elevated fasting glucose. Table 8 describes the definitions of the risk factors and the prevalence of MeS reported in the studies.

A single-centre study from Finland (93) reported the lowest prevalence of MeS compared to a multi-centre study from the US (82) and a single-centre study from Mexico (79). This could be partly explained by the different dosing of immunosuppressive medication among studies. The study from Finland (93) focused on the maintenance phase, when the immunosuppressive drug dosing was already reduced to a minimum, while the other two studies reported higher doses of immunosuppressive medication. It has been shown in previous studies that immunosuppressive medication (glucocorticoids) is associated with post-transplant

weight gain (83). As higher BMI is associated with higher prevalence of MeS (106), this may partly explain a higher prevalence of MeS in the other two studies.

The different study population provides another possible explanation of the difference of the prevalence of MeS between studies. The US study (82) reported a higher prevalence compared to the study from Finland (93). As the US population is more overweight compared to the European population (101), they are more prone to having a higher prevalence of MeS compared to European population. The Mexican study (79) is the only study that reported the patterns of multiple CVRFs. The more frequent combination was hypertension + hypertriglyceridemia + low HDL in four patients and one patient in each of the following combinations: hypertriglyceridemia + waist >95% + hypertension; glucose intolerance + waist >95 +low HDL; glucose intolerance + hypertriglyceridemia + low HDL.

Table 8. Definition and prevalence of metabolic syndrome reported in the studies

Authors (year)	**Definition of risk factors**				**Prevalence of MeS %** **(95% CI)**	**Time of measurement post Tx**
	Overweight	Hypertension	Abnormal lipids	Elevated fasting glucose		
Tainio et al. (2014)[93]	NR		NR	Fasting glucose>100 mg/dL	19 (14-24)	1.5 years
					14 (9.3-18)	5 years
Wilson et al. (2010)[82]	BMI>97th percentile for age and sex	BP>95th percentile for age and sex of the general US population or use of antihypertensive medication	HDL<5th percentile and TG>95th percentile for age and sex, or on lipid-modifying therapy.	Fasting glucose>100 mg/dL, or requirement for insulin or oral hypoglycemic therapy.	38 (33-43)	1 year
Ramirez-Cortes et al. (2009)[79]	Waist circumference >95% (75 cm)	BP>95th percentile for age and sex	HDL cholesterol< 10th percentile for age and sex, TG>90th percentile for age and sex	Fasting glucose>140 mg/dL	25 (9.9-40)	2 years

MeS-metabolic syndrome, HDL-cholesterol-high density lipoprotein cholesterol, TG-triglycerides, BMI-body mass index, BP-blood pressure, TX-transplantation. NR-not reported,

MeS was defined as minimum of three of the five criteria: overweight; hypertension; low HDL cholesterol; elevated TG; elevated fasting glucose. Number is superscript refers to the study identifier; CI-confidence interval

2.3.2 Part 2. Association of cardiovascular risk factors with all-cause mortality and cardiovascular outcomes in patients who initiated RRT in childhood. Systematic review

This systematic review presents results of the associations between CVRFs with all-cause mortality and CVD outcomes in patients who initiated RRT in childhood. Detailed characteristics of the studies included in the systematic review are presented in Table 4.

2.3.2.1 The association of anaemia or haemoglobin with all-cause mortality in patients who initiated RRT in childhood

Three studies (22, 71, 72) reported the association between anaemia or Hb levels and all-cause mortality. The number of patients in the studies ranged from 677 to 1,942. All three studies reported data collected from national and international renal registries such as the NAPRTCS (71), the USRDS (72) and the IPPN (22). The mean age ranged from 10.2 to 16 years. The studies were heterogeneous in terms of the incident or prevalent RRT population. Incident RRT patients are new patients who started RRT within a specified period (62). Prevalent RRT patients are patients who have already started RRT at a specified point in time (62). The NAPRTCS study included incident RRT patients who started on dialysis (PD and HD) (71). The USRDS included prevalent HD patients (72) and the IPPN study included incident and prevalent PD patients (22). The definitions of anaemia differed among the three studies. The NAPRTCS study defined anaemia as Ht<33% 30 days after initiation of dialysis (71). The USRDS defined anaemia as Hb<11 g/dl (72). The IPPN used Hb values as a continuous variable in their analysis (22).

A summary of the findings of the included studies of anaemia or Hb with all-cause mortality is presented in Table 9. The studies consistently showed that patients with lower Hb/Ht values had a higher risk of all-cause mortality compared to patients with higher levels of Hb/Ht.

Table 9. Results of included studies describing the association of anaemia or Hb and all-cause mortality in patients who initiated RRT in childhood

Author (year)	Follow-up time in years	Anaemia comparison groups	Effect estimate (95 CI)	Statistical method
Warady et al. (2003)[71]	Median 2.6 (IQR not reported)	Ht <33% Ht≥33%	1.52 (1.03-2.26) 1.00	Cox proportional-hazards regression model with RRT as a time-varying covariate
Amaral et al. (2005)[72]	Mean 2.1 (SD 1.3)	Hb≥11 g/dl Hb<11	0.38 (0.20-0.72) 1.00	Cox proportional-hazards regression model
Borzych-Duzalka et al. (2012)[22]	Median 0.8 (IQR 0.22-1.56)	Continuous	0.23 per g/dl, p<0.003, CI not reported	Cox proportional-hazards regression model with time-varying covariates

NAPRTCS- North American Pediatric Renal Transplant Cooperative Study, USRDS-United States Renal data system, IPPN-International Pediatric Peritoneal Dialysis Network, SD-standard deviation, IQR-inter quartile range, CI-confidence interval, Hb-haemoglobin, Ht-haematocrit. Number is superscript refers to the study identifier

The NAPRTCS study reported crude mortality rate in anaemic patients of 2.2 per 100 person-years (p/y) and in non-anaemic patients of 0.7 per 100 p/y. Anaemic patients receiving RRT had a 52 % higher risk of all-cause mortality compared to non-anaemic patients during a median follow-up of 2.6 years (IQR not reported) (71). The USRDS study reported mortality rate in anaemic patients to be 5.0 per 100 p/y and in non-anaemic patients to be 1.9 per 100 p/y. Non-anaemic patients had a 62% lower risk of

all-cause mortality compared to anaemic patients during a mean follow-up time of 2.1 years (SD 1.3) (72). The IPPN study reported 46 deaths but did not report a mortality rate. The authors modelled Hb as a continuous variable and showed that each 1 g/dl increase in Hb was associated with 77% lower risk of all-cause mortality (22) during a median follow-up of 0.8 years ((IQR) 0.22-1.56). The CI for the reported HR was not provided by authors. The large effect reported by the latter study could be in part explained by the method that was used in their analyses. The authors modelled Hb as a time-varying variable, meaning that Hb measurements of patients who died were taken close to patient`s date of death. Therefore, those measurements represent measurements taken from a sicker RRT population. In this case it may have led to an overestimation of the real association.

2.3.2.2 The association of BMI with all-cause mortality in patients who initiated RRT in childhood

Two observational studies (54, 107) described the association between BMI and all-cause mortality. The first study performed by the USRDS registry included 1,949 patients (107). The second study included data for 6,658 patients registered in the NAPRTCS registry (54). The studies differed in terms of type and duration of RRT and categorisation of BMI. The USRDS study included prevalent transplanted and dialysis patients at baseline (107), while the NAPRTCS study started follow-up at the time of transplant (54). The USRDS study reported BMI as SDS to standardise these with respect to age and sex. The resulting SDS for each individual patient reflects the number of SDs that the BMI of the patient differs from the average age and sex adjusted BMI from the general population (107). These calculated scores were modelled as a continuous variable in their analysis. The NAPRTCS study treated BMI

as a binary variable, defining obesity as a BMI greater than the 95th percentile for age and sex of the general population at time of transplantation (54). Both studies used normative reference data for BMI obtained from the age- and sex-matched general US population (108).

The results of these studies are presented in Table 10. The USRDS study reported 189 deaths, but did not report the mortality rate. The authors showed a U-shaped association between BMI and risk for all-cause mortality (p=0.001). Using the reference BMI SDS of 0.50, moving either above or below this point by one, two and three SDSs was associated with a 6%, 26% and 67% increased risk for all-cause mortality, respectively (107). The NAPRTCS study reported 385 deaths, but also did not report the mortality rate. Results from this study showed no difference in overall survival between obese and non-obese participants. However, stratified analysis by age groups showed an increased risk of all-cause mortality in 6-12 year old obese living donor and cadaver donor transplant recipients as compared to kidney donor recipients of the same age with a normal BMI, HR 3.65 (95 CI, 1.46-9.11) and 2.94 fold (95 CI, 1.53-5.63), respectively. The most common cause of death in this patient group was cardiopulmonary disease. No significant associations were found between obesity and all-cause mortality in patients younger than six or older than 12 years of age (54). The authors have stratified their analysis by donor source, presumably because other studies reported a higher risk of death in cadaver donor transplant recipients compared to living donor transplant recipients in children receiving RRT (109, 110).

Table 10. Results of included studies describing the association between BMI and all-cause mortality in patients who initiated RRT in childhood

Author (year)	Follow-up time in years	Obesity comparison groups	Effect estimate (95 CI)	Statistical method of analysis
Wong et al. (2000)[107]	Maximum 7 years	Continuous	Referent BMI SDS=0.50. aRR at ±1 SDS=1.06 (0.95-1.18); aRR at ±2 SDS= 1.26 (1.01-1.57); aRR at ±3 SDS=1.67 (1.14-2.45)	Cox proportional-hazards regression model
Hanevold et al. (2005)[54]	Mean 4.3 years (SD not reported)	BMI>95th percentile, BMI≤95th percentile (reference group)	**2-5 years old** aRR=0.38 (0.09-1.65) for living donor recipients and 0.45 (0.17-1.17) for cadaver donor recipients; **6-12 years old** aRR=3.65 (1.46-9.11) for living donor recipients and 2.94 (1.53-5.63) for cadaver donor recipients; **13-17 years old** aRR=1.03 (0.36-2.94) for living donor recipients and 0.44 (0.11-1.81) for cadaver donor recipients **All ages** aRR=1.15 (0.63-2.11) for living donor recipients and 1.17 (0.73-1.90) for cadaver donor recipients	Cox proportional-hazards regression model

BMI-body mass index, SD-standard deviation, SDS-standard deviation score, aRR-adjusted relative risk. Number is superscript refers to the study identifier

2.3.2.3 The association of hypertension with all-cause and cerebrovascular mortality in patients who initiated RRT in childhood

Two observational studies (53, 111) reported the association between hypertension and all-cause mortality. The first study, conducted by Groothoff et al. aimed to study and evaluate the late physical, social and psychological effects of ESRD (53). The authors included 249 patients from the Late Effects of Renal Insufficiency (LERIC) cohort. LERIC included all Dutch children younger than 15 years of age who started RRT between 1972 and 1992 and who had reached adulthood, defined as aged older than 18 years old, at the time of the study. The study was based on the National Dutch Registry of patients on RRT (53). The National Dutch Registry covers 100% of the RRT population in the Netherlands, as registration is compulsory. The second study, conducted by Kari et al. aimed to examine risk factors for RRT in children with CKD (stage 1-5) in Saudi Arabia (111). The authors included 1,000 children, treated in the King Abdulaziz University Hospital in Saudi Arabia between 2006 and 2014 (111).

These two studies were heterogeneous in terms of distribution of age, race, CKD stages and duration of follow-up. The population in the Dutch study (53) was older compared to the Saudi study (111), with the mean age at start of RRT being 10.6 years (range 1.9-14.9) and 4.9 (SD 4.3) years, respectively.

The Dutch study (53) did not report the race/ethnicity distribution in their study. Just over half of the population in the Saudi study (111) was of Saudi ethnicity, but the authors did not report the distribution of the other race/ethnic groups. The Dutch study (53) included patients receiving RRT (HD, PD, and transplanted patients), while the Saudi study (111) included patients with all stages of CKD (stage 1-5), mean eGFR

69.2 (SD 44.1) ml/min per 1.73m^2. The duration of follow-up was longer in the Dutch study (53) compared to the Saudi study (111) due to the fact that the Dutch study followed-up their cohort from the start of RRT in childhood into adulthood. The follow-up time was 15.5 years (SD not reported) and 1.5 years ((IQR) 0.4-4.0), in the Dutch and the Saudi studies, respectively. Both studies investigated the association of hypertension with all-cause mortality. The Dutch study (53) additionally explored the association of hypertension with cerebrovascular mortality. In both studies hypertension was defined as a SBP or DBP measurement above the 95th percentile of the general age, sex and height matched US population according to the Task Force on Blood Pressure in Children (112). The Dutch study (53) categorised hypertensive patients as follows: for each patient a ratio of total number of BPs with values above the 95th percentile divided by the total number of BPs with values below the 95th percentile was calculated. Patients with a ratio of more than one were categorized as patients with a "relatively long standing" hypertension. The Saudi study (111) define hypertension based on BPs at the start of follow-up. Results of these studies are presented in Table 11.

Table 11. Results of included studies describing the association of hypertension with all-cause and cerebrovascular mortality in patients who initiated RRT in childhood

Author (year)	Follow-up time in years	Hypertension comparison groups	Effect estimate (95 CI)	Statistical method of analysis
Groothoff et al. (2002)[53]	Average 15.5 years		All-cause mortality	
		BP >95th percentile for age, sex and height	3.1 (2.1-4.6)	Cox proportional-hazards regression model
		BP≤95th percentile	1.0	
			Cerebrovascular mortality	
		BP >95th percentile for age, sex and height	2.5 (1.0-6.7)	
		BP≤95th percentile	1.0	
Kari et al. (2015)[111]	Median 1.5 (IQR:0.4-4.0)		All-cause mortality	
		BP >95th percentile for age, sex and height	2.46 (1.66-3.65)	2 log-binominal regression model
		BP≤95th percentile	1.0	

BP-blood pressure, aRR-adjusted relative risk, IQR-interquartile range. Both studies reported association of hypertension with all-cause mortality, Groothoff et al additionally reported association of hypertension with cerebrovascular mortality. Number is superscript refers to the study identifier

Both studies reported that hypertensive patients had a higher risk of all-cause mortality compared to non-hypertensive patients. Additionally the Dutch study did not find a statistically significant association between hypertension and cerebrovascular mortality. Relative risk (RR) was 3.1 (95 CI, 2.1–4.6) and 2.5 (95 CI, 1.0-6.7) for all-cause and cerebrovascular mortality, respectively (53). The Saudi study reported that patients with hypertension had 2.46 times higher risk of all-cause mortality compared to patients with a normal BP, RR 2.46 (95 CI, 1.66-3.65)) (111). The authors did not provide a stratified analysis by CKD stages.

2.3.3 Quality assessment of the studies included in the literature and systematic review

The quality assessment of the studies included in the literature and systematic reviews was conducted using the CASP checklist. The questions of the CASP checklist were applied to assess the internal validity of the studies by identifying the potential for random error, selection and information bias in the studies, the role of confounding factors, as well as the assessment of the external validity of the studies. Questions relating to confounding factors were not applicable to studies reporting the prevalence of CVRFs included in the literature review. Table 12 shows a detailed description of the quality assessment of the studies included in the systematic review. The quality of the studies included in the literature and systematic reviews is discussed in the following section.

2.3.3.1 Internal validity of the studies

Internal validity of the studies can be affected by random error (chance), systematic error (bias) and confounding factors.

Potential role of chance or random error in the studies

None of the studies included in the literature review reported 95% CI for the prevalence estimates. It is, therefore, not possible to assess how precise their estimation is. Almost all studies included in the systematic review reported 95% CIs for HRs of the associations between CVRFs and all-cause and cerebrovascular mortality. Some 95% CIs were broad which means that there was not a reasonable statistical precision around the reported HRs. Moreover, there is a possibility of chance finding (Type 1 error) in the NAPRTCS study that reported the association of obesity

with all-cause mortality among transplanted patients as the authors performed multiple tests (54). The finding of the study of the higher risk of all-cause mortality in 6-12 year old obese compared to kidney donor recipients of the same age with a normal BMI may be due to chance. One of the approaches to minimise the possibility for random error to occur is to establish stricter threshold of the significance level, 99% CI or $p < 0.01$.

There is a possibility of Type 2 error in the Dutch study (53) that investigated the association of hypertension with cerebrovascular mortality. The authors did not find a statistically significant association that might be due to the lack of statistical power as the number of cerebrovascular events was too small (n=15) out of total 249 patients. This is reflected in a wide CI around obtained effect estimate (HR=2.5; 95% CI 1.0-6.7).

Only one study did not report the CI for the reported HR (22) making it difficult to determine the potential for random error. However, the authors did present the associated p-value that indicated statistical significance of this estimate at the $p<0.05$ level.

Table 12. Quality assessment using CASP checklist of the studies included in the systematic review

Question	Warady et al. (2003)	Amaral et al. (2005)	Borzych-Duzalka et al. (2012)	Wong et al. (2000)	Hanevold et al. (2005)	Groothoff et al. (2002)	Kari et al (2015)
CVRF and outcome	Anaemia and all-cause mortality	Anaemia and all-cause mortality	Haemoglobin and all-cause mortality	Obesity and all-cause mortality	Obesity and all-cause mortality	Hypertension and all-cause and cerebrovascular mortality	Hypertension and all-cause mortality
Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure accurately measured to minimise bias?	Can`t tell	Can`t tell	Can`t tell	Can`t tell	Can`t tell	Can`t tell	Can`t tell

Question	Warady et al. (2003)	Amaral et al. (2005)	Borzych-Duzalka et al. (2012)	Wong et al. (2000)	Hanevold et al. (2005)	Groothoff et al. (2002)	Kari et al (2015)
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Have the authors identified all important confounding factors? Which ones?	Yes Initiation year (continuous), gender, initiation age (categorical), race, treatment (time-varying covariate), diagnosis of ESRD, Iron use (Yes/no), EPO use (Yes/no).	Yes Age, race, sex, PRD, dialysis vintage, vascular access type, Medicare/Medic aid insurance status, serum albumin level, serum ferritin level, baseline hypertension, baseline eGFR by Schwartz, iron use, and EPO dose (quartiles).	No Serum albumin (continuous), PTH (log transformed, continuous), age at first observations in study (continuous), time on PD prior to study start (continuous), EPO type (Yes/no), EPO dose (continuous), cumulative number of peritonitis episodes	No Gender, race, duration of ESRD, treatment modality (time-varying covariate), height and stratified by age	Yes Race, gender, age, transplant year, antihypertensive drug use during the first 30 days, time between dialysis initiation and transplantation, HLA match, delayed graft function, and previous transplant status.	Not applicable, only crude effect size reported	No Age, gender and duration of follow-up

Question	Warady et al. (2003)	Amaral et al. (2005)	Borzych-Duzalka et al. (2012)	Wong et al. (2000)	Hanevold et al. (2005)	Groothoff et al. (2002)	Kari et al (2015)
			(continuous), biocompatible fluid (Yes/no).				
List the ones you think might be important, that the author missed	Comorbidities	Comorbidities	Sex, PRD, race, comorbidities	PRD, comorbidities	PRD, comorbidities	Age, gender, PRD, type of RRT, BMI, comorbidities	BMI, eGFR, comorbidities
Was the follow up of subjects complete enough?	Yes	Yes	Yes	Can`t tell (numbers of lost to follow-up not reported)	Can`t tell (numbers of lost to follow-up not reported)	Yes	No
Was the follow up of subjects long enough?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
How precise are the results?	Relatively narrow CI	Relatively narrow CI	Can`t tell, CI is not reported	Relatively narrow CI	Relatively narrow CI	Relatively narrow CI	Relatively narrow CI

Question	Warady et al. (2003)	Amaral et al. (2005)	Borzych-Duzalka et al. (2012)	Wong et al. (2000)	Hanevold et al. (2005)	Groothoff et al. (2002)	Kari et al (2015)
Do you believe the results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Do the results of this study fit with other available evidence?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

EPO-erythropoietin, eGFR-estimated glomerular filtration rate, PRD- primary renal disease, RRT-renal replacement therapy, BMI- body mass index, PTH-parathyroid hormone.

Potential role of systematic (bias) error in the studies

Bias can arise from the methods used to select the study population, factors affecting the study participation (selection bias) or from inaccuracy of the methods used when collecting information about an exposure or an outcome (information bias). Bias can lead to conclusions that underestimate or overestimate the true association between exposure and outcome (113). Potential for selection and information bias was identified in the majority of the studies included in the literature and systematic review.

Selection bias

Selection bias occurs when characteristics of individuals who were eligible for the study but not included are related to the exposure and, independently from the exposure, to the outcome. As a result, the association between exposure and outcome differs between individuals included in the study and non-participants (113). The potential for several types of selection bias was identified in the studies included in the literature and systematic review and include: incidence-prevalence bias (Neyman bias or survival bias); volunteer bias; and loss to follow-up bias.

Incidence-prevalence bias

Incidence-prevalence bias is a type of selection bias that occurs when we try to estimate the risk of a disease on the basis of data collected at a given time point in a series of survivors rather than on data gathered during a certain time period in a group of incident cases (113).

The majority of the studies included in the literature review were cross-sectional studies of patients with varying duration of RRT (prevalent RRT) who are, by definition, survivors to the time of the study. Some studies in the systematic review

also included prevalent RRT populations (22, 72, 107, 111). Excluded patients who started RRT at the same time as patients included in the study but who have died before reaching the study point might be left out of the study. It is not possible to know whether characteristics of patients at start of RRT differ between those who survived to participate in the studies and those who did not because the information is not provided by the authors. For this reason, it is impossible to identify the direction of selection bias and its possible effect on the internal validity of the studies. If the patients that were left out of the study were sicker and had a higher prevalence of CVRFs compared to patients who were included in the study, the authors may have underestimated the true prevalence of CVRFs. On the other hand, the authors might have overestimated the true prevalence of CVRFs if prevalence of CVRFs increases with duration of RRT. Similarly, the associations of anaemia (22, 72), obesity (107) and hypertension (111) with all-cause mortality might have been underestimated or overestimated depending on the direction of the bias.

The Dutch study (53) that investigated the association of hypertension with all-cause and cerebrovascular mortality by design is affected by survival bias. The authors included patients who started RRT in childhood and reached 18 years old by the time of the study. If patients who died before reaching adulthood were hypertensive, exclusion of non-survivors might have led to underestimation of the true association between hypertension and all-cause and cerebrovascular mortality in childhood-onset RRT.

Volunteer bias

Volunteer bias (or self-selection bias) occurs when individuals who volunteer for a study differ in relevant clinical characteristics from those who do not (113). There may be a potential source for volunteer bias in the studies that involved voluntary contribution of data to registries such as in the NAPRTCS and IPPN registries (22, 54, 71). As participating centres of both registries are asked to provide clinical data of consenting patients, there might be a potential for both patient and centre-level volunteer bias. According to Ganguli et al. (114) mortality rate is much lower in volunteers from the general population than in those who are recruited through intensive enrolment efforts. However, in the population of sick children it might be that the parents of ill children are more willing to volunteer and participate in the study, as they may be more conscious in regard to the health of their children. On the other hand, parents may be less likely to consent if their child is critically ill, as they may be too anxious and stressed to want to join a study. The information about the non-participating patients/centres was lacking and because of this it was not possible to identify the effect of volunteer bias on the internal validity of the studies. In both scenarios the prevalence of anaemia (22, 71), obesity (54) and hypertension (96) and the associations of anaemia (22, 71) and obesity (54) with all-cause mortality reported by these registries would be different in participants compared to the broader population of children receiving RRT.

Loss to follow-up bias

Loss-to-follow-up bias frequently occurs in prospective cohort studies (113). The potential for loss to follow-up bias has been identified in one study form Saudi Arabia

included in the systematic review (111). There were 37.3% of patients who were lost to follow-up. If the proportion of deaths was higher among those lost to follow-up and more of these patients were hypertensive, the true HR of the association between hypertension and all-cause mortality would be underestimated. However, due to the lack of the information about patients who were lost to follow up, it was not possible to identify the direction of the loss to follow-up bias and its effect on the internal validity of the study.

There may be a potential source for selection bias in the studies included in the literature and systematic review conducted by the USRDS registry (72, 107) given that the outcome data (deaths and hospital admissions) are only available for patients who have Medicare coverage. Patients without Medicare coverage were not included in the studies and might represent significantly sicker patients with a higher prevalence of CVRFs because of the delay with the start of RRT compared to patients who started RRT on time. Moreover, these patients might have died before they became eligible for Medicare coverage and initiated their RRT treatment. In this case the true HRs of the association might have been underestimated. However, according to the USRDS registry, 92% of US patients have Medicare coverage, therefore, it is unlikely that a large underestimation of the true association could have occurred (17). The characteristics of other 8% of patients are not reported by the registry.

Patients with missing data were excluded from analyses in the majority of the studies included in the literature review. However, the characteristics of the excluded patients are not provided by all studies, it was therefore, not possible to identify the direction of selection bias and its effect on the internal validity of the studies. In the systematic review missing data were reported in two studies, the IPPN study (22) and the USRDS

study (107). The IPPN study (22) investigated the association of Hb with all-cause mortality. The authors stated that the information on Hb was available for all patients. However, the data on ESA (erythropoiesis-stimulating agents) dose were missing in 25% of participants. As the association of Hb and all-cause mortality in this study was adjusted for ESA dose, 25% of patients were not included in regression models adjusted for this variable. The association may be underestimated if excluded patients represented those who had lower Hb values due to poor treatment and had an increased risk of death compared to included patients. However, if excluded patients had adequate treatment and, therefore, higher Hb levels and additionally had lower death rate compared to included patients the association might be overestimated. Unfortunately, the characteristics of patients with missing data were not described by the authors. In contrast, the USRDS study provided information about 40% of the patients that they excluded from the analysis due to missing patient identifier, key demographic data or height/weight measurements (107). The authors reported that there were no statistically significant differences between the two groups in mortality rate and patient characteristics (115). Therefore, it is unlikely that exclusion of patients with missing data may have biased their results.

Information bias

Information bias occurs during data collection with the most common type being misclassification bias, which occurs when the detection of the exposure status or outcome (disease) assessment is biased. Exposed/diseased patients are classified as non-exposed/non-diseased and vice-versa. Misclassification can be differential or non-differential. In differential misclassification, the exposure or outcome identification

differs between comparison groups, while in non-differential misclassification it is the same in both groups (113).

The potential for misclassification of exposure status might occur in multicentre/registry studies if some participating centres have used laboratory and/or instrumental methods that might lead to misclassification of exposure status. Detailed description of different methods of Hb/Ht determination and BP measurements are described in the literature review. Since automated haematology analyser and casual BP tend to underestimate the true prevalence of anaemia and hypertension compared to Hb cyanide method and ABPM methods, the resulting prevalence of risk factors might be underestimated in the studies included in the literature review. In terms of the studies included in the systematic review, this misclassification is likely to be non-differential, which leads to attenuation of the effect size towards the null.

Additionally, there may be potential for overestimation of BMI, BP and anaemic status in studies including dialysis patients due to fluid overload and shifts in plasma volume (73). Unfortunately, the information about the timing of the measurement relative to the timing of dialysis was only available in a small number of studies. Studies conducted by the ESPN/ERA-EDTA registry (37, 64) that are included in the literature review, reported that the registry collects dry body weight. Dry weight is the body weight at the end of dialysis at which the patient can remain normotensive until the next dialysis (116). Therefore, it is unlikely that the BMI would be overestimated. However, the authors might have potentially overestimated the prevalence of hypertension, as the registry collects pre-dialysis BP. The USRDS study (107) included in the systematic review reported that the USRD registry also collects dry body weight in dialysis patients. Therefore, it is unlikely that the large overestimation

of BMI occurred. If authors overestimated the BMI of the dialysis patients, the misclassification is likely to be non-differential among those with the outcome and those without, biasing the HR of the association between BMI and all-cause mortality towards one.

In terms of the potential misclassification of the outcome data in the studies included in the systematic review, it is unlikely that the all-cause mortality would be misclassified among participants who were not lost to follow-up. All included national registries collect mortality data obtained from the medical records and submitted by the participating centres. However, there is always a potential for misclassification of cause-specific mortality on deaths certificates. There was only one study conducted by Groothoff et al. (53) that studied cerebrovascular disease mortality. The authors visited 37 hospitals in the Netherlands in order to collect all available information from medical records on the cause of death and so their classification is likely to have been valid.

Confounding

Confounding exists where an apparent association between an exposure and an outcome of interest is partly or entirely explained by a third variable. It is important to identify relevant confounders and adjust for the confounding effect as much as possible. There are three criteria that need to be fulfilled to determine whether a variable could be considered a potential confounder:

- the variable needs to be associated with the exposure
- the variable needs to be associated with the outcome
- the variable should not be an intermediate variable on the causal pathway between exposure and outcome

In observational studies confounding can be minimised during the design of a study by restriction or matching, or if this is not possible, it can be controlled during the analysis by stratification or adjustment (117).

Adjustment for a variety of potential confounders was performed in six out of seven studies included in the systematic review, but only the Dutch study (49) reported crude effect estimates. Age at start of RRT, type of RRT and duration of RRT were adjusted for in all studies of the systematic review where appropriate.

Age at start of RRT was taken into account in all studies, as younger age is associated with a higher prevalence of anaemia and hypertension, while obesity and dyslipidaemia are more common among older children. Also, younger children receiving RRT have a higher risk of death compared to older children (118). Additionally, age is not on the causal pathway in the association between CVRFs and all-cause mortality.

Two studies of the systematic review adjusted their analyses for type of RRT, the NAPRTCS (71) and the USRDS (107) studies, as both included a mixed RRT population (HD, PD and transplanted patients). However, this variable might be on the causal pathway, as sicker patients with comorbidities are more likely to start on HD and healthier patients are more likely to receive a kidney transplant. Presumably, the authors aimed to investigate the associations of anaemia (71) and obesity (107) with all-cause mortality independently from the type of RRT. However, by adjusting for variable that is on the causal pathway the intermediate effect that goes through this variable is removed (117).

Three studies adjusted their analyses for duration of RRT: two studies from the USRDS (72, 107) and the IPPN (22) registry, as the authors included prevalent RRT populations with varying durations of therapy. The NAPRTCS (54) also adjusted their analysis for duration of dialysis before receiving a kidney transplantation as they included transplanted population (119).

PRD is another important confounding factor (120) but, only three out of six studies adjusted for it (71, 72, 111). The use of iron and ESA medication was adjusted for in all three studies describing the association of anaemia with all-cause mortality (22, 71, 72). However, this variable might lie in the causal pathway in this association, as patients with lower Hb values are more likely to be prescribed iron or ESA medication compared to patients with normal Hb levels. Similarly, the NAPRTCS (54) might have over-adjusted their analysis by controlling the association of obesity with all-cause mortality for the use of antihypertensive drugs as hypertension might lie on a potential causal pathway (61).

The Saudi study that investigated the association of hypertension with all-cause mortality (111) included patients with different stages of CKD. However, the authors did not control their analyses for eGFR level. Furthermore, this study also did not account for BMI level. It is known that obesity is associated with both high BP (64) and all-cause mortality (107) in children receiving RRT and it is not on the causal pathway in this association.

2.3.3.2 External validity of the studies

Unfortunately, it was not possible to assess the external validity of the single-centre studies included in the literature and systematic reviews. It is hard to draw conclusions

about the generalisability of their results due to the lack of the information about the national coverage of the general population in their countries by the single centres. If single-centres are not representative of the whole RRT population of their country the results obtained by these studies cannot be generalizable to a wider RRT population of the whole country.

Moreover, a single-centre study conducted by Kari et al. (111) included in the systematic review, comprised children with all stages of CKD (1-5). However, it might be that those patients with early stages of CKD who were referred to their hospital might represent a more ill CKD population, as early stages of the disease are usually asymptomatic (121). Therefore, the results might not be generalizable to all patients with early stages of CKD. Additionally, 53.9% of patients in this study were Saudi nationality and, therefore, the results of this study may not be generalizable to a population of patients with different ethnic distribution.

The multi-centre studies included in the literature and systematic reviews were mainly performed by the national renal registries, the ESPN/ERA-EDTA, the USRDS, the NAPRCTS, the IPPN and the National Dutch Registry. The detailed description and the coverage of the general population by the ESPN/ERA-EDTA, the USRDS, the NAPRCTS and the IPPN are presented in the "Introduction" chapter. Briefly, the ESPN/ERA-EDTA registry reported a high coverage of the general European population by the registry and, therefore, their results might be broadly generalizable to the European countries participating in the registry and to the entire European population of patients receiving RRT (18). The USRDS registry covers all patients with ESRD in the US. However, the specific types of analyses are restricted to

Medicare patients (17) and, therefore, the results of this registry can only be extrapolated to the Medicare eligible population.

The IPPN and the NAPRTCS are both voluntarily collected data. The response proportion in the IPPN registry differed between countries (10% US; 19% Turkey; 31% European countries; 59% Canada; 80-90% Chile, Korea, Argentina; 100% China, Finland, Singapore, Macedonia, Nicaragua, Uruguay) (22). The information of the coverage by the NAPRTCS is not reported. For both registries it is difficult to say how representative they are to the total paediatric RRT population of the participating countries as I have not found such information available either on the websites or in their publications. Moreover, participating countries in the IPPN registry differ, therefore, generalisability of overall results to specific countries might be difficult.

The study performed by Groothoff et al. (49), described in the systematic review, used data from the National Dutch Registry of patients on RRT. The authors included all Dutch patients as the registration in the registry is compulsory. Therefore, this study represents a good generalisability of their results to all paediatric RRT patients who survive to adulthood in the Netherlands.

The majority of studies included in the literature review of the prevalence of CVRFs included transplanted patients. Three studies (14, 15, 17) reporting the association between anaemia or Hb levels and all-cause mortality included only dialysis populations. The NAPRTCS study describing the association of obesity with all-cause mortality included patients after kidney transplantation. Therefore, the results of these studies are not representative to the entire population of patients who initiated RRT in childhood. The Dutch study investigating the association of hypertension with all-

cause and cerebrovascular mortality included patients who started RRT in childhood and reached 18 years old by the time of the study, therefore, the results cannot be extrapolated to patients who started RRT in childhood but did not survive to adulthood.

2.4 Discussion

2.4.1. Findings of the literature review and limitations of the studies

The identified studies reported a high prevalence of CVRFs in patients who initiated RRT in childhood. Although the prevalence of CVRFs is high, the overall range of the prevalence was broad across studies for all CVRFs. The fact that the studies differed largely from each other in terms of their inclusion criteria of the study population, RRT population, definition of the exposure and the methods used to determine the CVRFs likely contributed to this heterogeneity, making it difficult to compare findings across studies. Furthermore, due to the potential for selection and misclassification bias, identified in all studies, their internal validity might be compromised, resulting in overestimation or underestimation of the reported prevalence.

Most of the identified studies were from single hospitals and included selected RRT populations either receiving dialysis or after kidney transplantation with the majority of information available from the studies on transplanted patients. Furthermore, the timing of kidney transplantation differed largely across studies making it difficult to extrapolate the results to patients after receiving a kidney transplant. The fact that the majority of studies included transplanted patients might be explained by the fact that over time the majority of patients with ESRD receive a kidney transplant. Only studies performed by the ESPN/ERA-EDTA registry included both dialysis and transplanted population and reported the prevalence of hypertension, obesity and dyslipidaemia stratified by RRT modality. Their results showed that the prevalence of hypertension and dyslipidaemia was higher among the dialysis population compared to transplanted

population, while prevalence of obesity was higher after kidney transplantation compared to dialysis population. However, this registry showed the prevalence of anaemia only in dialysis patients. No studies showed that the prevalence of anaemia differs by type of RRT.

Few studies described the combinations of traditional CVRFs combined in MeS (hypertension, overweight, dyslipidaemia and increased fasting glucose). No studies described the combinations of traditional and uraemia-related CVRFs. Therefore, it is not clear whether the prevalence and combinations of traditional and uraemia-related CVRFs differs between patients receiving dialysis and after kidney transplantation.

2.4.2. Findings of the systematic review and limitations of the studies

Despite the high prevalence of CVRFs a limited number of studies were found that investigated the associations of anaemia, obesity and hypertension with all-cause mortality in patients with childhood-onset RRT. No studies reported the association between dyslipidaemia and all-cause mortality. Furthermore, there is a big gap in the literature about the associations of CVRFs with CVD outcomes. Only one study was found that reported the association between hypertension and cerebrovascular mortality.

In general, the studies included in the systematic review were heterogeneous by RRT type, inclusion of incident or prevalent patients, characterisation of the exposure and adjusted covariates. Therefore, it would be inappropriate to combine the data to obtain overall summary effect estimates. Furthermore, the follow-up was relatively short in most studies. Moreover, insufficient information on aspects such as characteristics of non-participants and methods of CVRFs measurements prevented identification of

possible bias. For example, the lack of information about the numbers and characteristics of missing patients and patients who were lost to follow-up made it impossible to identify the role of selection bias in majority of the studies. Also the information on methods of measurements of CVRFs was not available in all studies, probably due to the lack of such records in the registries. Most studies accounted for important confounding factors, however, some other important confounders (for example eGFR level) were not taken into account by the authors. Similar to the studies included in the literature review, most of the studies of the systematic review were performed on a selected RRT population either receiving dialysis, or after kidney transplantation or specific age group, which limits generalisability of their results to all RRT population.

The lack of studies describing association between CVRFs and all-cause mortality or CVD outcomes is partly explained by the rarity of ESRD in children and a small number of deaths limiting the power of the studies. Additionally it can be explained by the lack of access to cause specific mortality data in patients with childhood-onset RRT to reliably describe cause-specific mortality. Moreover, there might be a potential for publication bias, as studies that failed to achieve statistically significant results might not be published. The investigators of identified studies were not contacted to request any unpublished results. Therefore, it might be that non-significant results were not published and only significant association was reported in publications.

No RCTs were identified by our search strategy. However, RCTs would be valuable in order to know whether lowering BP to less than 95th percentile of age and sex specific values by using antihypertensive therapy, or achieving Hb levels higher than 11 g/dl by using EPO reduces risk of all-cause or CV mortality. The lack of placebo

controlled RCTs can be explained by the ethical reasons that cannot allow children to be left untreated. Another option would be to conduct no-placebo controlled trials testing whether different dosage of drugs will achieve the target BP and Hb levels. Due to the lack of such trials in children receiving RRT current guidelines on management of CVRFs in these patients are extrapolated from data collected in adults with ESRD.

2.4.3. Limitations of the literature and systematic review

One search strategy was used for both parts of the literature review. This search was specifically designed to systematically search for papers reporting on the associations of CVRFs with outcomes of interest. However, the papers that were identified through this search strategy reporting the prevalence of CVRFs were included in the literature review. Therefore, given the non-comprehensive search for studies reporting the prevalence of CVRFs, it is possible that relevant papers on prevalence of CVRFs in populations with childhood-onset RRT may not have been identified by the search strategy. However, studies performed by large national and international renal registries that reported the prevalence of CVRFs have been identified by the search suggesting that key information has been included in the literature review. Additionally, the specific search terms to identify studies reporting the prevalence of abnormal mineral metabolism in patients with childhood-onset RRT were not included in the search strategy and, therefore, included studies might represent selective papers reporting this information.

Other databases such as the nursing data base CINAHL, the Latin American database LILACS and the Chinese databases were not searched, and only English language papers were sought. Therefore, not all relevant studies might have been identified.

However, most relevant studies in this area are likely to be published in English and in journals that are included in Medline or Embase because the major registries studies are within English speaking countries or European countries where scientific research is usually published in English language journals. Moreover, the annual reports of the national and international renal registries were read as the grey literature; however, they did not add any relevant information.

2.4.4. Future research

Study design and sample size of future studies

Since ESRD in children is a rare condition, it is extremely difficult to recruit a sufficient number of patients to RCTs and prospective cohort studies. Therefore, the most feasible study design for future research would be retrospective cohort studies using routine national renal registry data. In order to increase a sample size of future studies data from several national renal registries should be combined. For example, one of the best sources of routinely collected clinical data of patients who initiated RRT in childhood in Europe is the ESPN/ERA-EDTA registry, which collects data via the national and regional renal registries. Currently 38 European countries provide their data to the registry. The international nature of the registry allows including large number of patients to the studies. The main limitations of this study design are: the retrospective nature of the study and possibility of missing relevant data; the restriction to only those countries that collect the relevant routine renal data.

Data to be collected by the registries for future research

The individual national renal registries have to collect data on CVRFs such as BP, BMI, lipids, Ca, P, PTH and Hb for all patients at the start of RRT. Measuring CVRFs

at the start of RRT is important in order to minimise incident-prevalence bias in future research. Furthermore, data on medications (antihypertensive medication, iron and EPO use, statins, and immunosuppressive medication) has to be recorded to adjust for it in future analyses. Previous studies included in the literature review used different definitions of CVRFs making it difficult to compare findings between each other. For example, inclusion of antihypertensive medication into the definition of hypertension may have resulted in overestimation of the prevalence of hypertension as patients with controlled BP are categorised as hypertensive compared to studies that used BP level alone. In future, renal registries should choose a standard definition of hypertension in order to improve comparability of their findings. Adopting a definition of hypertension without including antihypertensive medication would be more appropriate to avoid any overestimation of the estimates. The same applies to the definitions of other CVRFs, for example, anaemia and dyslipidaemia.

Furthermore, previous studies varied by methods of measurements of CVRFs, which also resulted in variability of reported estimates. For example, some studies used pre-dialysis BP, while other studies used post-dialysis. Pre-dialysis BP measurements tend to overestimate the prevalence of hypertension due to fluid overload compared to post-dialysis BP measurements. Similarly, studies that used Ht rather than Hb measurements to define anaemia reported a higher prevalence as Ht is less accurate method. Therefore, renal registries should also standardise methods of measurements of CVRFs. Collecting post-dialysis rather than pre-dialysis BP measurements and Hb rather than Ht will allow to minimise bias in future research and improve comparability between studies.

Not all confounding factors were accounted for in previous studies. In future, renal registries have to collect data on main confounding factors such as PRD, comorbidities, race/ethnicity and social-economic status.

There is a big gap in current knowledge about CVD incidence among children receiving RRT. It might be because access to morbidity data was difficult to gain for previous studies. Therefore, in future, it is important to establish a data linkage between routine renal registries data and hospital admissions data in order to study CVD incidence in this population.

2.5 Conclusion

In conclusion, the literature review showed that the information about the prevalence of CVRFs in patients with childhood-onset RRT is sparse and derived from selected populations of patients, mostly after kidney transplantation, performed by single-centre studies. Available studies are heterogeneous by RRT population, definition and methods used to determine CVRFs. Additionally, to my knowledge, no studies exist describing the combinations of traditional and uraemia-related CVRFs in patients with childhood-onset RRT.

The systematic review identified limited evidence for the association of CVRFs with all-cause mortality. Available studies included a selected population of RRT patients and with a relatively short follow-up period. Additionally, there is a big gap in knowledge about the associations of CVRFs with CVD outcomes (morbidity and mortality) in patients with childhood-onset RRT.

The next chapter of my thesis is the ESPN/ERA-EDTA registry analyses that describes the prevalence and patterns of CVRFs and their association with all-cause and CV mortality in patients who initiated RRT from 0-20 years old in Europe.

Chapter 3. Prevalence and patterns of cardiovascular risk factors and their association with all-cause and cardiovascular mortality in young European RRT patients; ESPN/ERA-EDTA registry analysis

This chapter introduces the ESPN/ERA-EDTA registry and gives a justification for using this data source. It also describes the methods used for the data analysis, results obtained and contains a discussion of the findings.

3.1 Introduction

The results of the literature review presented in the previous chapter showed that only limited information is available about the prevalence and patterns of CVRFs in patients who initiated RRT in childhood. Most of the available information about the prevalence of CVRFs is based on single-centre studies with the majority only including kidney transplant patients. Therefore, the available studies do not represent the whole RRT population. The results of the systematic review showed that only a few studies have investigated the association between CVRFs and all-cause mortality. Most of the available studies were conducted in selected RRT populations either including dialysis or kidney transplant patients. In most studies only a short follow-up was available. Moreover, there is a very limited knowledge about the association of CVRFs with CV morbidity and mortality in patients who initiated RRT in childhood. To illustrate, the systematic review identified only one study reporting the association of hypertension with cerebrovascular mortality in patients who initiated RRT in childhood and survived into adulthood (29).

Some of the identified gaps in the literature will be addressed in this chapter by analysing data from a large international paediatric renal data source-the ESPN/ERA-

EDTA registry. This is an international renal registry, based in Amsterdam, the Netherlands, which annually collects information on patients from 0 to 20 years of age, receiving RRT (dialysis and kidney transplantation) in Europe. Currently, 38 European countries voluntarily provide data to the registry. The data collection comprises information on date of birth, sex, PRD, treatment modality, date of first RRT, changes of RRT, death and cause of death, as well as a variable set of anthropometric, biochemical and medication-related data. All data are collected during routine clinical care (18).

To analyse the ESPN/ERA-EDTA registry data I submitted a project proposal to the registry board in order to request permission. The ESPN/ERA-EDTA registry data can only be accessed from their office in Amsterdam as part of their data protection policy. I received permission to access the ESPN/ERA-EDTA data in Amsterdam for a restricted time period, from 1st of March until 31st of May 2015.

I focused my analyses on the following four CVRFs - hypertension, abnormal BMI, dyslipidaemia and anaemia. These four CVRFs were chosen due to practical reasons. First, because of restricted time of the data access in Amsterdam I needed to limit the number of CVRFs of interest. Second, these four CVRFs were the most complete recorded variables in the ESPN/ERA-EDTA registry. Data on Ca, P and PTH levels was not very complete. Therefore, abnormal mineral metabolism was not addressed in these analyses.

The specific objectives of this work were as follows:

1. To describe the prevalence of individual CVRFs (hypertension, abnormal BMI, dyslipidaemia and anaemia) in patients registered in the ESPN/ERA-EDTA registry.

2. To describe combinations of multiple CVRFs in patients registered in the ESPN/ERA-EDTA registry.

3. To investigate the association between individual CVRFs and all-cause and CV mortality in patients registered in the ESPN/ERA-EDTA registry.

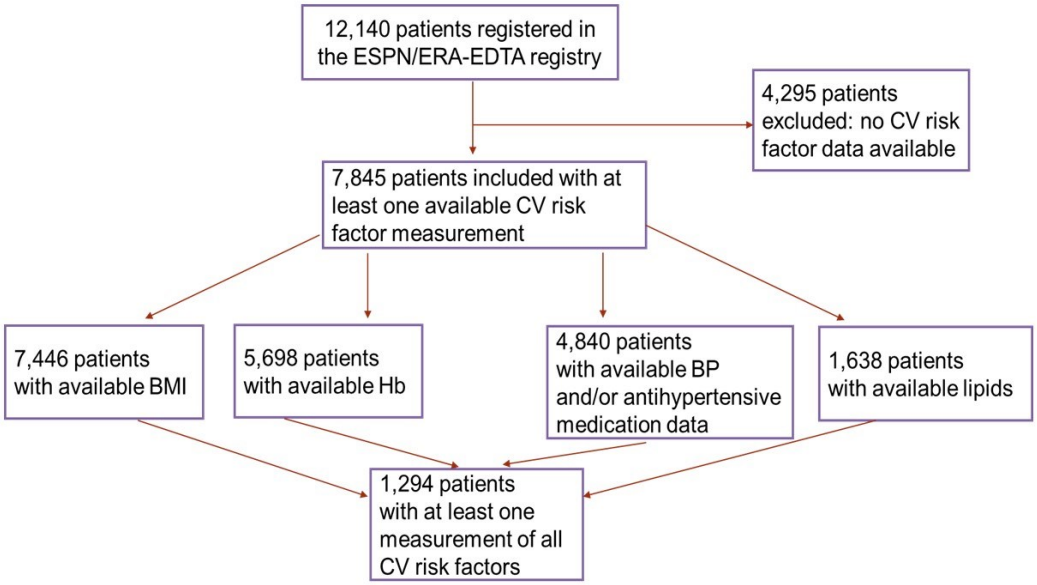
3.2. Methods

3.2.1 Patients

For the current study, data regarding age at start of RRT, sex, PRD, type of RRT, SBP and DBP, use of antihypertensive medication, BMI, Hb, total cholesterol, HDL cholesterol, TG, cause and date of death were extracted from the ESPN/ERA-EDTA registry. Only for a small proportion of the patients CVRFs measured at the start of RRT were available. Therefore, incident and prevalent RRT patients and all their available CVRFs measurements during the period from the start of RRT until 31st December 2012 were included in the analyses. This resulted in the inclusion of 7,845 out of a total of 12,140 patients registered in the ESPN/ERA-EDTA registry, who had at least one CVRF measurement (Figure 9).

Weight and height measurements were most complete, while the largest proportion of missing data was among lipid fractions. 7,446 patients were included in the BMI analysis; 5,698 patients in the analysis of anaemia; 4,840 patients in the hypertension analysis; 1,638 patients were included for the dyslipidaemia analysis. For the description of the prevalence of multiple CVRFs and their combinations, patients who had at least one measurement of all four CVRFs were included, resulting in 1,294 patients.

Figure 9. Flow chart describing availability of CVRFs measurements in patients receiving RRT, registered in the ESPN/ERA-EDTA registry by 31 December 2012



3.2.2 Countries

Data from 33 European countries reported between 1992 to 2012 were included for the current study. This included data from the following countries and periods: Albania (2010-2012), Austria (2010-2012), Belgium (1996-2012), Bulgaria (2008-2012), Belarus (2008-2012), Switzerland (1980-2012), Czech Republic (2007-2012), Germany (2010-2012), Denmark (2000-2012), Estonia (2008-2012), Spain (1991-2012), Finland (1992-2011), France (2004-2012), Greece (1997-2012), Croatia (2008-2010), Hungary (2008-2012), Iceland (2002-2010), Italy (1995-2012), Lithuania (2007-2012), Moldova (2011), Montenegro (2008), Macedonia (2007-2012), the Netherlands (2004-2012), Norway (2006-2012), Poland (2008-2012), Portugal (2007-2012), Romania (2008), Serbia (2007-2012), Russia (2007-2012), Slovenia (2008-2012), Slovakia (2007-2012), Turkey (2010-2012), and the UK (1992-2012). Data from five countries (Cyprus, Georgia, Israel, Latvia and Sweden) were excluded from

the present analyses as these countries did not have any records of CVRFs measurements.

For the analysis, different European countries were combined into four European regions based on the genetic similarities of the European population (122) as follows:

East: Albania, Austria, Belarus, Bulgaria, Croatia, Czech Republic, Estonia, Macedonia, Greece, Hungary, Lithuania, Moldova, Montenegro, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, Turkey

West: Belgium, France, Switzerland, the Netherlands, the United Kingdom, Germany

North: Denmark, Finland, Iceland, Norway

South: Spain, Portugal, Italy

Coverage of general population by individual registries

The majority of the individual European registries which provide data to the ESPN/ERA-EDTA cover 100% of the eligible population of the country, except Czech Republic, Poland and Russia, which cover 99%, 98% and 99% of the eligible population, respectively (123). However, for the current analyses patients have been selected based on the available data on the CVRFs of interest.

3.2.3 Age groups

Patients and young adults were categorised into four age groups, using categories used in previous ESPN/ERA-EDTA publications: 0-<2 years old; 2-<6 years old; 6-<12 and 12-20 years old. The youngest category of 0-<2 years old was kept separately as previous studies have shown a higher mortality risk in this age group compared to older patients (118). Other age groups have been classified based on the periods of a

child`s development: preschool 2-<6 years old, school age 6-<12 years old and teenagers and young adults 12-20 years old (37, 40). Furthermore, using the previous used ESPN/ERA-EDTA age categories makes comparisons between earlier published results possible.

3.2.4 Definitions of CVRFs

Definition of dyslipidaemia

Dyslipidaemia was defined by the presence of at least one of the following criteria based on definitions derived from guidelines for CV health and risk reduction in children and adolescents (124):

- Hypertriglyceridaemia:
    (a) 0-9 years: TG >100 mg/dL (>1.1 mmol/L)
    (b) 10-20 years: TG >130 mg/dL (>1.5 mmol/L)
- Low HDL cholesterol: <40 mg/dL or <1.0 mmol/L
- High non-HDL cholesterol calculated as total cholesterol minus HDL-cholesterol: >145 mg/dL or >3.7 mmol/L

Definition of hypertension

Hypertension was defined according to the Fourth report on the diagnosis, evaluation, and treatment of high BP in children and adolescents (125):

SBP and/or DBP≥95th percentile for sex, age, and height (SDS≥1.65), or use of antihypertensive medication.

Definition of underweight and overweight/obesity

BMI was calculated as weight (kg)/height $(m)^2$. For 0–<2 year old patients BMI was categorised according to age- and sex-specific criteria of the World Health Organization (WHO) (126-128):

- underweight (BMI SDS ≤ −2 SDS)
- normal weight (−2 < BMI SDS ≤ +2)
- overweight (+2 < BMI SDS ≤ +3)
- obesity (BMI SDS > +3)

The WHO reference is based on the United States` children. The SDS were already calculated in the dataset I received for the analysis.

To categorise BMI for patients older than 2 years old, cut-off values from the International Obesity Task Force were used (129, 130). These age- and sex-specific cut-off values are based on centile curves passing through adult health related cut-off points for underweight (BMI of <17 kg/m^2), overweight (BMI of 25-29.9 kg/m^2) and obesity (BMI of ≥30 kg/m^2) at the age of 18 years.

Definition of anaemia

Anaemia was defined based on an amalgamation of the European guidelines for patients on PD (131), the 2011 UK National Institute for Health and care Excellence (NICE) guidelines for patients with CKD (132), the European guidelines for adults and the Food and Drug Administration (FDA) guidelines (133):

- Hb<10.5 g/dL for patients younger than 2 years
- Hb<11.0 g/dL for patients of 2 years or older

3.2.5 Causes of death

Individual national registries defined causes of death according to the ERA-EDTA coding system, which are subsequently classified into the following groups; CV, infection, malignancies, haemorrhage, other and unknown (123).

The present analyses are focused on CV mortality that included the following causes of death:

- Myocardial ischaemia and infarction
- Hyperkalaemia
- Haemorrhagic pericarditis
- Other causes of cardiac failure
- Cardiac arrest / sudden death
- Hypertensive cardiac failure
- Hypokalaemia
- Fluid overload / pulmonary oedema
- Pulmonary embolus
- Cerebrovascular accident
- Mesenteric infarction

3.2.6 Statistical analysis

For each patient Hb, BP, TG and non-HDL-cholesterol values above the normal range or below for HDL-cholesterol were coded as 1, where values in normal range were coded as 0. BMI measurements were first classified into three groups as underweight, normal weight and overweight/obesity. After that I created two variables. To indicate underweight measurements normal and overweight/obese BMI measurements were coded as 0 and underweight measurements as 1. To indicate overweight/obese

measurements normal and underweight measurements were coded as 0 and overweight/obese measurements as 1.

To summarise the prevalence of CVRFs from repeated measurements, the sum of each binary definition was divided by the total number of available measurements for this specific patient. This resulted in a weighted average. For example, if a patient had three BP measurements, of which two were in the hypertensive range and one in the normotensive range, these measurements were summarised as (1+1+0)/3 = 0.67. Values equal to or above 0.5 were used to identify hypertension. A similar process was used for the other CVRFs and RRT modality. A similar approach to summarise repeated measurements into one weighted value was used in a previous analysis (29).

Chi square tests were used to investigate any differences in prevalence of CVRFs between groups of patients. When more than 20% of the expected numbers were less than 5, Fisher`s exact tests were used (134).

To describe the association between CVRFs and all-cause and CV mortality, Kaplan-Meier plots were used to describe crude survival probabilities. In the analyses focusing on the association of CVRFs with CV mortality patients who died from other causes of death were censored.

Cox proportional-hazards models were used to estimate the relative mortality risk of patients with the CVRF compared to patients without the CVRF. Patients without the CVRF of interest were chosen as the reference category due to the lower risk of mortality based on the reviewed literature. The main assumption in the Cox model is the proportionality of hazards which means that the survival curves must have hazard functions that are proportional over time (135). The proportional hazard assumption

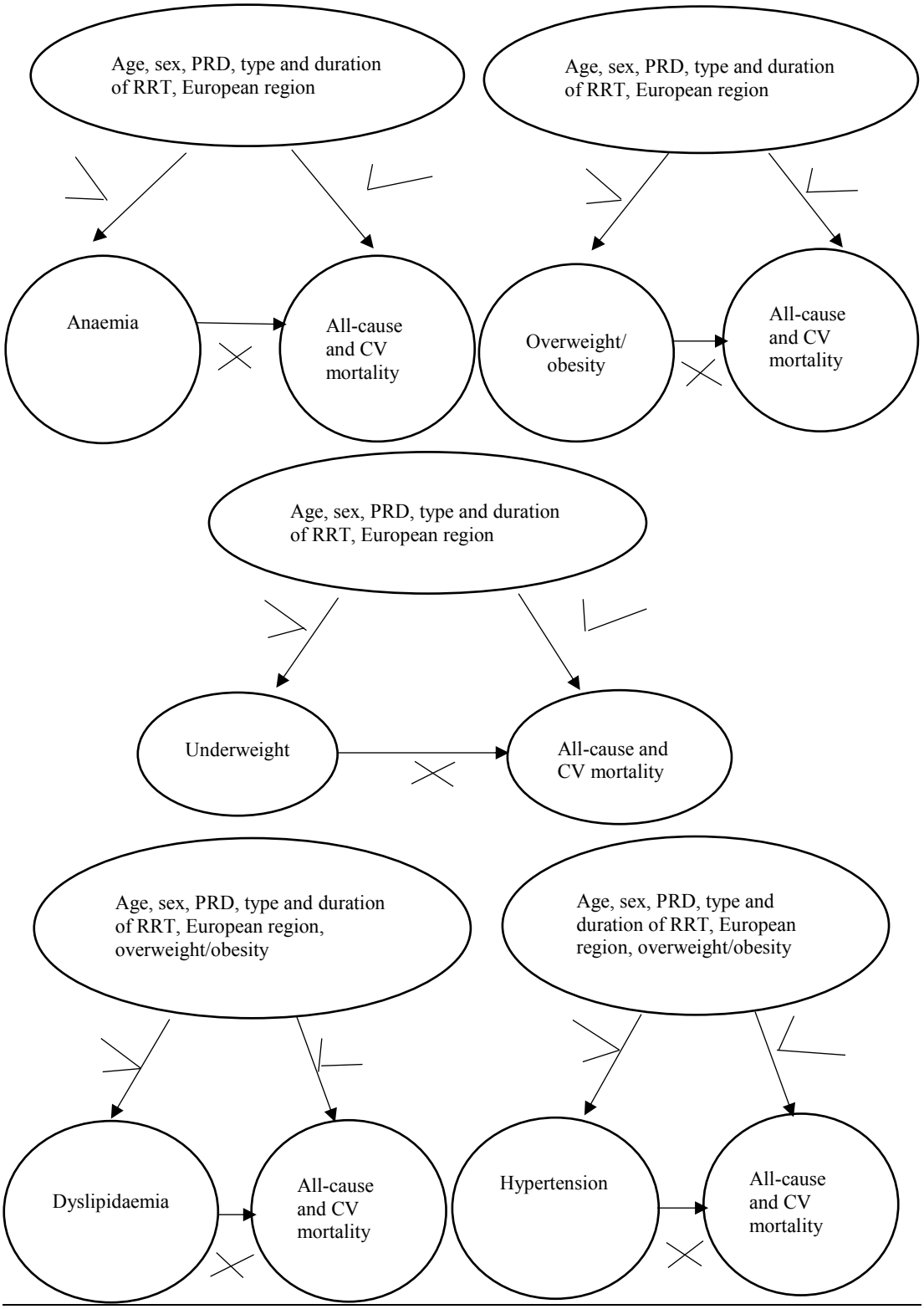
was evaluated graphically using log minus log plots. The log minus log plots should result in parallel curves if the proportional assumption is not violated. Where the proportionality assumption was violated, the follow-up period was split according to the crossing point of survival curves (135).

Each CVRF was assessed in a crude (univariate) Cox proportional hazards model. Thereafter, multivariable analyses investigating the association of the individual CVRFs with all-cause and CV mortality were conducted. Since there were no CV deaths in the non-dyslipidaemic group it was not possible to perform Cox proportional hazards analysis to determine the association between dyslipidaemia and CV mortality. Figure 10 illustrates the approach taken to adjust for potential confounding factors (136). In this figure tick means that the confounding factor is associated with the exposure and with the outcome, while cross means that the confounding is not on the causal pathway of this association. Each individual association of CVRFs with all-cause and CV mortality was adjusted for age at start of RRT, sex, PRD, type and duration of RRT and European region. Associations of hypertension with all-cause and CV mortality and dyslipidaemia with all-cause mortality were additionally adjusted for overweight/obesity. This is justified because obesity is associated with higher risk of hypertension and dyslipidaemia and independently from them it is associated with higher risk of mortality. Furthermore, obesity is not on the casual pathway in these associations, therefore, it is a potential confounding factor. In contrast, the association of obesity with all-cause and CV mortality has not been adjusted for hypertension and dyslipidaemia as they might be part of the causal pathway of this association. Adjusting for the variable that lies in the casual pathway might lead to underestimation

or overestimation of the true HR. Results of the crude and adjusted models are presented as unadjusted and adjusted HRs, respectively.

The start of the follow-up period was the date of the first measurement of the CVRFs and the end of follow-up was December 31st 2012 (the most recent available end-point), death, loss to follow-up, or reaching 20 years of age, whichever came first. It was not possible to extend the follow-up period after patient reaching 20 years of age, as the ESPN/ERA-EDTA only collects data on patients receiving RRT from 0 to 20 years old. Data for patients older than 20 years old are collected through the adult part of the ERA-EDTA registry. However, due to the absence of data linkage between the paediatric and adult parts of the ERA-EDTA registries it was not possible to describe outcomes among patients after reaching 20 years of age.

Figure 10. Schematic overview of adjusting for potential confounding factors in the associations between individual CVRFs with all-cause and CV mortality



3.2.7 Planned sensitivity analysis

For the primary analyses all available CVRFs measurements per patient during follow-up were included in the analysis. However, measurements of CVRFs recorded close to death are not likely to be representative predictors of the outcome but rather a marker of the severity of the underlying pathology. Therefore, a broad window of six months has been chosen to make sure that measurements that were taken close to death will not influence the results. A planned sensitivity analysis was conducted excluding measurements taken in the last six months before death. If patients had CVRFs measurements taken within six months before death and longer, only the CVRFs measurements in the six months window before death were excluded. In case patients had all their CVRFs measurements taken within six month before death, these patients were excluded from the sensitivity analysis. This resulted in the exclusion of 84 patients whose CVRFs measurements were only available in the last six months before death. The prevalence of CVRFs and survival analysis were then repeated after exclusion of those measurements and patients and results have been compared to the primary analysis.

3.3 Results

3.3.1 Patient characteristics

An overview of the collected data on CVRFs measurements collected by participating countries which are included in the current study is presented in Table 13. The UK, Spain, Italy, France, Russia and Switzerland contributed the majority of the data. In total 20 countries contributed data for all four CVRFs. For the other 13 countries data

was not available for all four CVRFs. See Table 13 for details of the contributing countries.

Table 13. Number and proportion of patients in the ESPN/ERA-EDTA Registry, who have at least one measurement of one CVRF by 31 December 2012 stratified by country

Country	N	Start year	HDL %	Chol %	TG %	SBP %	DBP %	Use of AHT %	BMI %	Hb %	Countries with all CVRFs
Albania	5	2010							100		
Austria	127	2010	-	-	-	-	-	98.4	98.4	21.3	
Belgium	168	1996	-	-	-	71.4	71.4	-	99.4	-	
Bulgaria	31	2008	-	-	-	-	-	-	100	-	
Belarus	46	2008	19.6	43.5	43.5	52.2	52.2	52.2	100	43.5	+
Switzerland	314	1980	1.3	3.5	3.2	63.7	63.7	29.3	98.1	61.5	+
Czech Republic	52	2007	19.2	38.5	36.5	63.5	63.5	50.0	100	40.4	+
Germany	35	2010	31.4	31.4	25.7	80.0	80.0	80.0	100	80.0	+
Denmark	216	2000	29.2	32.9	29.6	-	-	-	-	99.5	
Estonia	3	2008	100	100	100	100	100	100	100	100	+
Spain	1283	1991	-	-	-	63.7	63.7	84.8	99.8	64.4	
Finland	287	1992	81.5	86.4	81.2	95.5	95.5	-	99.7	82.3	+
France	660	2004	-	-	-	-	-	-	90.7	94.5	
Greece	96	1997	44.8	86.5	86.5	85.4	85.4	62.5	98.9	86.5	+
Croatia	5	2008	40.0	40.0	60.0	100	100	20.0	100	100	+
Hungary	48	2008	33.3	70.8	70.8	79.2	79.2	83.3	93.7	89.6	+
Iceland	4	2002	-	-	-	100	100	-	100	100	
Italy	759	1995	-	-	-	86.9	7.8	81.8	94.3	53.2	

Country	N	Start year	HDL %	Chol %	TG %	SBP %	DBP %	Use of AHT %	BMI %	Hb %	Countries with all CVRFs
Lithuania	20	2007	60.0	80.0	70	85.0	85.0	80.0	100	85.0	+
Moldova	1	2011	-	-	-	-	-	-	100	-	
Montenegro	3	2008	-	-	-	-	-	-	100	-	
Macedonia	6	2007	-	100	100	100	100	83.3	100	100	+
Netherlands	188	2004	73.9	79.3	80.9	98.4	98.4	98.9	100	74.5	+
Norway	88	2006	80.7	87.2	-	97.7	97.7	100	96.6	100	+
Poland	227	2008	66.9	76.2	73.1	95.2	95.2	4.8	99.6	80.6	+
Portugal	109	2007	86.2	88.9	88.1	88.1	88.1	85.3	100	89.9	+
Romania	30	2008	-	-	-	100	100	100	100	100	
Serbia	37	2007	-	83.8	83.8	81.1	81.1	86.5	100	94.6	+
Russia	420	2007	-	-	-	-	-	-	99.7	19.8	
Slovenia	14	2008	85.7	85.7	85.7	100	100	100	100	100	+
Slovakia	29	2007	20.7	41.4	41.4	41.4	41.4	41.4	100	41.4	+
Turkey	242	2010	-	36.4	35.9	73.6	73.9	51.7	91.7	48.3	+
United Kingdom	2292	1992	-	59.5	42.8	90.9	72.6	60.8	98.4	93.4	+
Total	**7845**		**10.1**	**31.4**	**25.0**	**66.3**	**60.8**	**51.2**	**94.8**	**72.7**	**20**

N-total number of patients, HDL-high density lipoprotein cholesterol, Chol-total cholesterol, TG-triglycerides, AHT-antihypertensive medication, SBP-systolic blood pressure, DBP-diastolic blood pressure, BMI-body mass index, Hb-haemoglobin

The characteristics of the total cohort of patients (N=7,845) are summarised in Table 14. The mean age of the included patients was 9.5 years (SE 0.06). The majority of patients were between 12 and 20 years old (39.8%) and 58.9% of the patients were male. PD was the most common type of dialysis therapy at the start of RRT (44.8%) and the most common PRD was CAKUT (40.8%).

Characteristics of the subset of patients with available CVRFs compared to those with missing CVRFs data are summarised in Table 15. Patients with missing data were slightly older compared to those with available data. Patients with missing data in all groups of CVRFs more often started on HD compared to those with available CVRF data. The proportion of pre-emptively transplanted patients was higher in patients with available BP and Hb compared to patients with missing BP and Hb. In contrast, the proportion of pre-emptively transplanted patients was lower in patients with available BMI and dyslipidemia compared with patients with missing data on those CVRFs. The proportion of deaths was larger among patients with missing data in all groups of CVRFs compared to patients with available data. Patients with missing lipids and Hb measurements had significantly higher proportions of deaths from CV disease, haemorrhage, infection and malignancies compared to patients with available records of lipids and Hb.

Table 14. Baseline characteristics of patients

Characteristics	N (%)
Age at start of RRT (years)	
0-<2	1,210 (15.4)
2-<6	1,205 (15.4)
6-<12	2,300 (29.3)
12-20	3,123 (39.8)
Missing	7 (0.1)
Sex	
Male	4,617 (58.9)
Initial type of RRT	
HD	2,775 (35.4)
PD	3,518 (44.8)
Tx	1,359 (17.3)
Unknown/missing	193 (2.5)
PRD	
CAKUT	3,202 (40.8)
GN	1,237 (15.8)
Cystic Kidney Disease	787 (10.0)
Hereditary Nephropathy	594 (7.6)
Ischaemic Renal Failure	137 (1.7)
HUS	314 (4.0)
Metabolic Disorders	273 (3.5)
Vasculitis	171 (2.2)
Miscellaneous	578 (7.4)
Unknown/missing	552 (7.0)

N-total number of patients who had at least one measurement of one of the four CVRFs, n-number of patients in subgroups, RRT- renal replacement therapy; HD- haemodialysis; PD- peritoneal dialysis; Tx- renal transplant; PRD-primary renal disease, CAKUT-congenital anomalies of the kidney and urinary tract; GN-glomerulonephritis, HUS- haemolytic-uremic syndrome.

Table 15. Characteristics of the study population with and without available CVRFs measurements. Characteristics are presented in percentages apart from mean age at start of RRT and total number of death

Characteristics	**BP/AHT+** **N=4,840**	**BP/AHT-** **N=3,005**	**BMI +** **N=7,446**	**BMI -** **N=399**	**Lipids +** **N=1,638**	**Lipids -** **N=6,207**	**Hb +** **N=5,698**	**Hb -** **N=2, 147**
Mean age at start of RRT in years (SE)	8.6 (0.08)	10.9 (0.1)	9.4 (0.07)	11.5 (0.31)	8.2 (0.14)	9.8 (0.07)	9.2 (0.08)	10.2 (0.11)
Missing	0.1	0.1	0.1	-	0.1	0.1	0.1	0.1
Sex								
Female	41.0	41.4	41.2	40.4	42.3	40.8	41.2	40.9
Male	59.0	58.6	58.8	59.6	57.7	59.2	58.8	59.1
Initial type of RRT*								
HD	29.0	45.6	34.7	47.1	26.4	42.0	33.0	41.8
PD	50.5	35.7	45.6	30.3	55.4	37.7	46.0	41.6
Tx	18.8	14.9	17.3	18.5	15.8	17.7	18.0	15.5
Unknown/missing	1.7	3.8	2.4	4.0	2.4	2.6	3.0	1.2
PRD								
CAKUT	41.7	39.3	41.3	30.1	39.3	41.1	40.1	42.7
GN	15.7	15.7	15.6	18.7	14.4	16.1	15.8	15.4
Cystic Kidney Disease	10.7	8.9	10.2	6.7	9.8	10.1	9.7	10.8
Hereditary Nephropathy	8.3	6.2	7.6	5.5	12.2	6.3	7.7	7.0
Ischaemic Renal Failure	2.1	1.2	1.7	1.0	1.8	1.7	1.8	1.3
HUS	3.8	4.2	4.1	4.0	3.2	4.2	3.9	4.1
Metabolic Disorders	3.5	3.3	3.5	2.7	2.8	3.6	3.2	4.1
Vasculitis	1.9	2.5	2.1	4.5	1.6	2.3	2.1	2.4
Miscellaneous	6.2	9.1	7.2	9.7	7.8	7.2	7.5	6.8
Unknown/missing	5.7	9.1	6.5	16.7	6.7	7.1	7.7	5.0
Proportion of all-cause death*	3.3	6.5	4.3	9.0	2.6	5.1	3.8	6.7
Distribution of cause of death*								
Total number of deaths (N)	162	195	321	36	43	314	214	143
Cardiovascular	24.1	21.5	14.6	19.4	16.3	23.5	18.2	29.4
Hemorrhage	3.7	5.1	4.7	2.8	2.3	4.8	3.3	6.3
Infection	20.9	18.9	19.3	16.7	9.3	21.3	16.8	24.5
Malignancies	6.8	4.6	5.9	2.8	2.3	6.1	4.7	6.9
Other known cause	19.1	25.6	22.4	25.0	25.6	22.3	27.6	15.4
Unknown	25.3	24.1	23.7	33.3	44.2	21.9	29.4	17.5

N-total number of patients, RRT-renal replacement therapy, SE-standard error, HD-haemodialysis, PD-peritoneal dialysis, Tx-transplantation, PRD-primary renal disease, CAKUT-congenital anomalies of kidney and urinary tract, GN- glomerulonephritis, HUS-haemolytic uremic syndrome, BP-blood pressure, AH medication- antihypertensive medication, BMI-body mass index, Hb-haemoglobin, *****indicates statistically significant association ($p<0.05$) between groups of comparison (distribution of causes of death was <0.05 only between patients with missing lipids and Hb measurements compared to patients with available records of lipids and Hb).

3.3.2 Prevalence of single CVRFs in young European RRT patients

The overall prevalence of dyslipidaemia, hypertension, anaemia, overweight and underweight is presented in Table 16.

Table 16. Overall prevalence of CVRFs

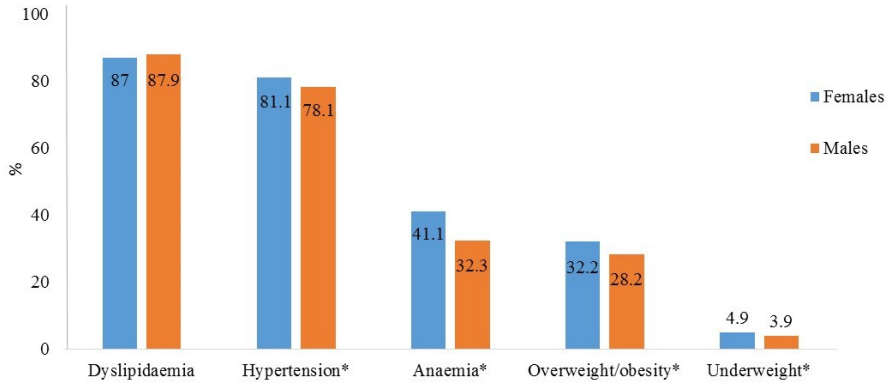
CVRFs	Total population	Prevalence %
Dyslipidaemia	1638	87.5
Hypertension	4840	79.3
Anaemia	5698	36.0
Overweight/obesity	7446	29.9
Underweight	7446	4.3

CVRFs-cardiovascular risk factors

The prevalence of CVRFs stratified by sex, age groups at start of RRT, type of RRT, PRD and European region is presented in Figures 10-13 and Table 17.

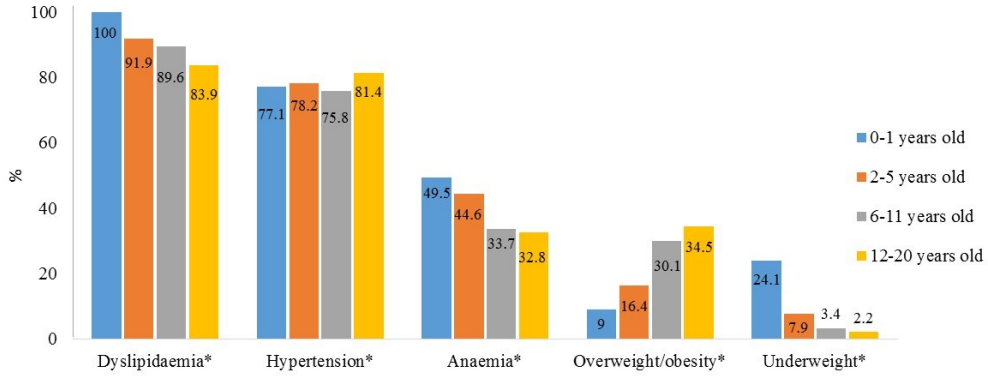
No significant sex differences were found in the prevalence of dyslipidaemia, however there was a statistically significant larger proportion of female patients among hypertensive, anaemic, overweight/obese and underweight patients (Figure 11). When stratified by age at start of RRT, dyslipidaemia, anaemia and underweight were more common among younger patients compared to older ones, while older patients were more frequently hypertensive and overweight/obese compared to younger patients (Figure 12).

Figure 11. Prevalence of CVRFs stratified by sex



Cardiovascular risk factors, * p value<0.05 for the differences between groups of comparison

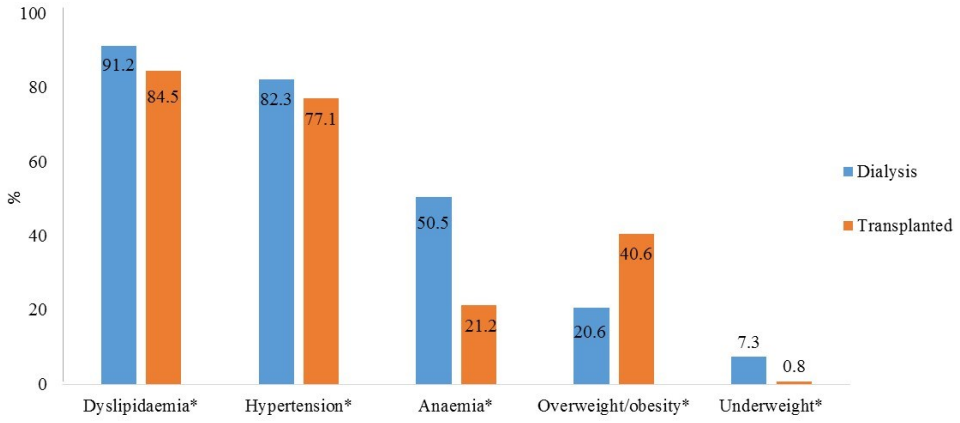
Figure 12. Prevalence of CVRFs stratified by age at start of RRT



Cardiovascular risk factors, * p value<0.05 for the differences between groups of comparisons

The prevalence of CVRFs stratified by modality of RRT (see Methods section page 141 for more information) is depicted in Figure 13. Most CVRFs were more prevalent among patients receiving dialysis compared to transplanted patients, while overweight/obesity was more common in patients after kidney transplantation.

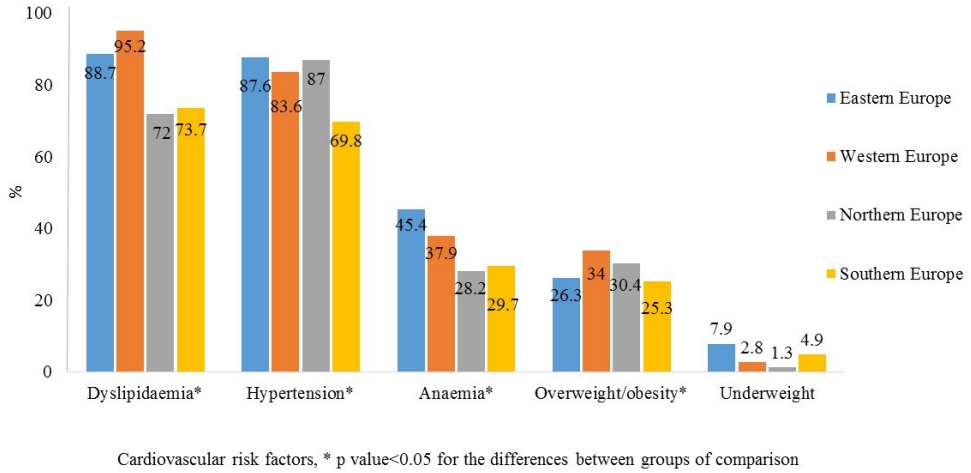
Figure 13. Prevalence of CVRFs stratified by modality of RRT



Cardiovascular risk factors, * p value<0.05 for the differences between groups of comparison

The stratified analysis of the prevalence of CVRFs by European region is shown in Figure 14. Dyslipidaemia and anaemia were more prevalent among Western and Eastern parts of Europe compared to the Southern and Northern part of Europe. The prevalence of hypertension was similar across the regions except a lower prevalence in the Southern region. Overweight/obesity was found to be more prevalent among Western and Northern European regions, compared to Eastern and Southern regions. The proportion of underweight patients was higher in Eastern and Southern regions, compared to Western and Northern European regions.

Figure 14. Prevalence of CVRFs stratified by European region



Cardiovascular risk factors, * p value<0.05 for the differences between groups of comparison

Table 17 shows the prevalence of the CVRFs by PRD. Patients with vasculitis and GN had a higher prevalence of hypertension and anaemia compared to patients with other types of PRD. Patients with cystic kidney disease and CAKUT were more frequently overweight/obese, while dyslipidaemia and underweight were more common among patients with metabolic disorders and ischemic renal failure, respectively.

Table 17. Prevalence of CVRFs stratified by PRD

PRD	Dyslipidaemia*	Hypertension*	Anaemia*	Overweight/ obesity*	Underweight
	%	%	%	%	%
CAKUT	89.1	72.6	31.3	32.6	3.2
GN	90.3	89.7	42.1	27.4	4.0
Cystic Kidney Disease	84.5	80.7	30.9	35.4	4.3
Hereditary Nephropathy	81.5	84.9	37.7	23.1	6.3
Ischaemic Renal Failure	90.0	68.0	29.0	24.1	10.5
HUS	90.6	82.4	38.7	19.5	3.7
Metabolic Disorders	100	80.1	38.4	31.7	3.4
Vasculitis	92.6	92.5	45.8	27.5	2.6
Miscellaneous	82.8	81.9	40.9	25.6	5.8
Unknown/missing	84.7	83.4	43.7	30.3	7.6

PRD-primary renal disease, CAKUT-congenital anomalies of kidney and urinary tract, GN-glomerulonephritis, HUS-haemolotic uraemic syndrome,

* p value<0.05 for the difference in the prevalence of CVRFs between PRD groups

In summary, the results show that dyslipidaemia, hypertension, anaemia and overweight/obesity are common among young European RRT patients. Younger patients have a higher prevalence of dyslipidaemia, anaemia and underweight compared to older ones, while older patients were more frequently hypertensive and overweight/obese compared to younger patients. Dyslipidaemia, anaemia, hypertension and underweight were more prevalent among patients receiving dialysis, while overweight/obesity was more common in patients after kidney transplantation. Eastern Europe had the highest prevalence of all CVRFs apart from overweight/obesity. The prevalence of overweight/obesity was higher among Western and Northern Europe compared to Eastern and Southern regions of Europe.

3.3.3 Prevalence and patterns of multiple CVRFs in European patients receiving RRT

As described in the methods the patterns of multiple CVRFs are studied in a cohort of patients with data available for all four CVRFs. The characteristics of this sub-cohort are compared to the excluded patients for whom at least one CVRFs measurement was missing (Table 18). There were no statistically significant differences between patients with missing data and available data in terms of sex and PRD distribution. However, patients with all available CVRFs were significantly younger at the start of RRT and started more frequently on PD compared to excluded patients. Also, a lower proportion of patients with all available CVRFs had received pre-emptive transplantation compared to patients with at least one missing measurement of CVRFs.

Figure 14 shows the numbers of CVRFs stratified by type of RRT. This figure shows that combinations of two and three CVRFs were more common, compared to none,

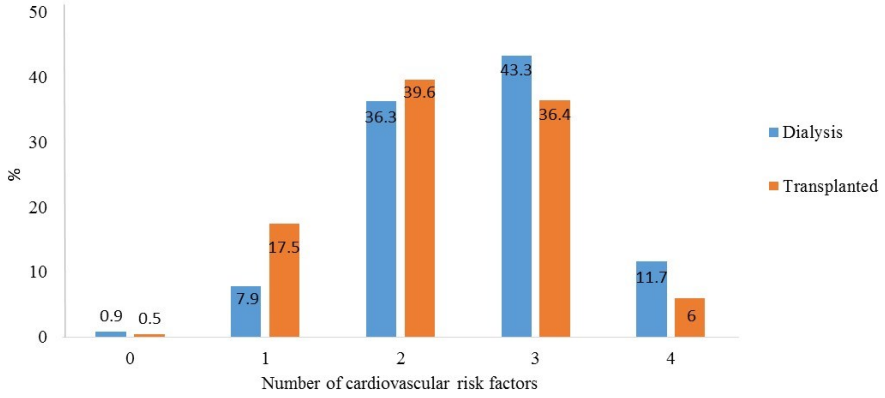
one and all four CVRFs on dialysis and after kidney transplantation. Dialysis patients have on average more CVRFs compared with transplanted patients (Figure 15).

Table 18. Characteristics of patients who had all CVRFs measurements available compared to patients with missing CVRFs data

Characteristics	**All CVRFs+ N=1,294 n (%)**	**All CVRFs- N=6,551 n (%)**
Age at start of RRT (years)*		
0-<2	302 (23.3)	365 (5.6)
2-<6	250 (19.3)	712 (10.9)
6-<12	375 (29.0)	1530 (23.4)
12-20	366 (28.3)	3942 (60.2)
Missing	1 (0.1)	-
Sex		
Male	743 (57.4)	3874 (59.1)
Initial type of RRT*		
HD	324 (25.1)	2451 (37.4)
PD	762 (58.9)	2753 (42.0)
Tx	180 (13.9)	1179 (18.0)
Unknown/missing	28 (2.1)	168 (2.6)
PRD		
CAKUT	505 (39.0)	2,697 (41.2)
GN	198 (15.3)	1039 (15.8)
Cystic Kidney Disease	125 (9.7)	662 (10.1)
Hereditary Nephropathy	180 (13.9)	414 (6.3)
Ischaemic Renal Failure	27 (2.1)	110 (1.7)
HUS	51 (3.9)	263 (4.0)
Metabolic Disorders	34 (2.6)	239 (3.7)
Vasculitis	20 (1.5)	151 (2.4)
Miscellaneous	89 (6.9)	489 (7.4)
Unknown/missing	65(5.0)	487 (7.4)

N-total number of patients, n-number of patients in subgroups, RRT-renal replacement therapy; HD-haemodialysis; PD-peritoneal dialysis; Tx-renal transplant; PRD-primary renal disease, CAKUT-congenital anomalies of the kidney and urinary tract; GN-glomerulonephritis, HUS-haemolytic-uremic syndrome, *indicates statistically significant association ($p<0.05$) between groups.

Figure 15. Number of CVRFs stratified by type of RRT



The combinations of CVRFs stratified by type of RRT are presented in Venn diagrams (percentages are not proportional to a corresponding areas of the eclipses) (Figures 16 and 17). For more detailed information about the numbers of patients within each stratum in patients on dialysis and after kidney transplantation can be found in Appendix 1, Tables 1 and 2, page 354. After stratifying by type of RRT the combination of dyslipidaemia, hypertension and overweight/obesity was more common among transplanted patients than among patients on dialysis (25.6% and 11.0% respectively), while the combination of dyslipidaemia, hypertension and anaemia was more common among dialysis than in transplanted patients (28.0% and 8.7% respectively) (Figures 16 and 17).

Figure 16. Venn diagram of multiple CVRFs prevalence in dialysis patients

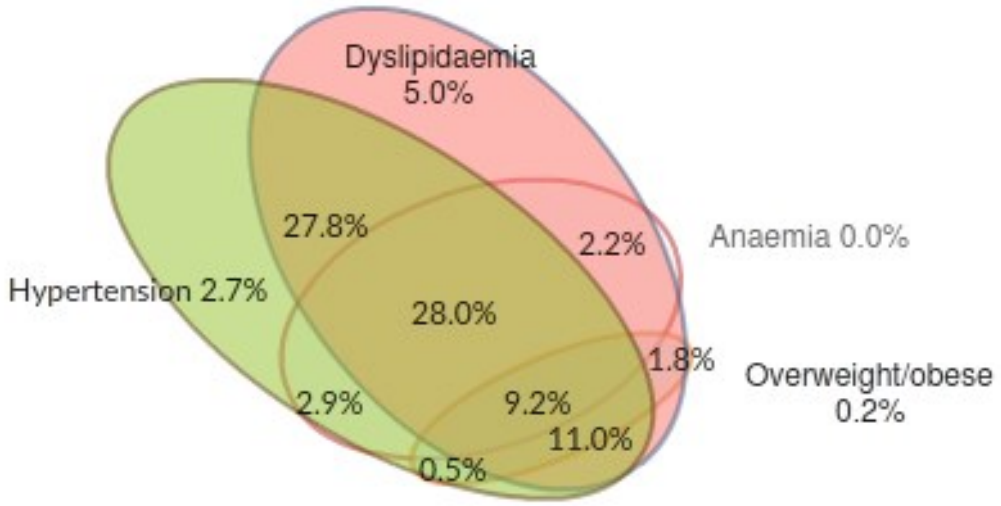
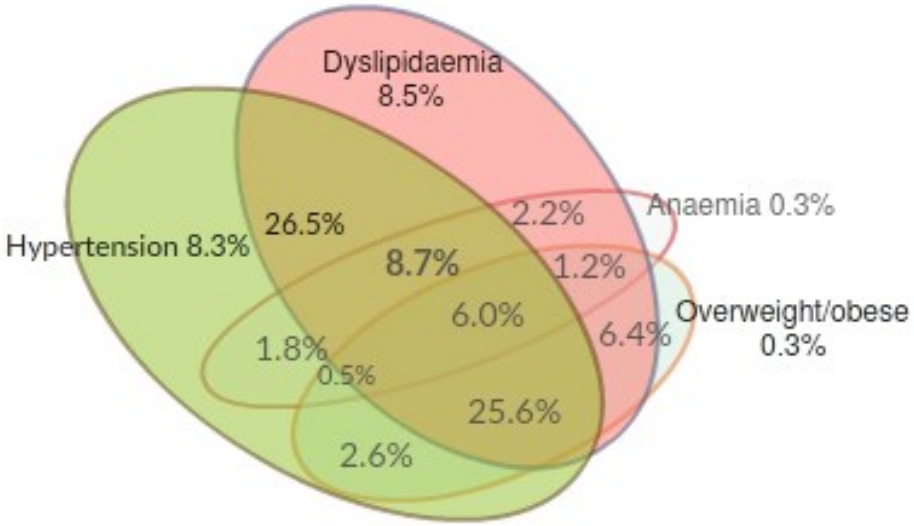


Figure 17. Venn diagram of multiple CVRFs prevalence in patients following transplantation



In summary, the results show that combinations of two and three CVRFs are more common, compared to none, one and all four CVRFs. The combination of dyslipidaemia, hypertension and overweight/obesity was more common among transplanted patients, while the combination of dyslipidaemia, hypertension and anaemia was more common among dialysis patients.

3.3.3 All-cause mortality and association between CVRFs and all-cause and CV mortality in patients who initiated RRT in childhood

Among all 7,845 patients there was a total of 37,494 patient-years of follow-up. The median follow-up was 3.7 years (IQR 1.7-6.8) and in total 357 patients died. The overall crude mortality rate was 9.5 (95% CI 8.5-10.5) per 1000 p/y. Mortality rates for different causes of death are presented in Table 19. Among known causes of death CVD and infections were the most common causes of death. Among other causes of death patients more often died from uraemia caused by graft failure and withdrawal of ESRD treatment for medical reasons.

Table 19. Numbers and cause-specific mortality rates of patients included in the ESPN/ERA-EDTA registry by 31 December 2012

Cause of death	N	Crude MR per 1000 p/y (95%CI)
All-cause	357	9.5 (8.5-10.5)
CVD	81	2.1 (1.6-2.6)
Infections	71	1.9 (1.5-2.3)
Malignancies	20	0.5 (0.3-0.7)
Haemorrhage	16	0.4 (0.2-0.6)
Other	81	2.1 (1.6-2.6)
Unknown	88	2.3 (1.8-2.8)

N-number of deaths, CVD-cardiovascular disease, MR-mortality rate

Table 20 describes the numbers and proportion of different types of CV death for patients in the ESPN/ERA-EDTA registry. The most common CV causes of death were cerebrovascular accident and cardiac arrest/ sudden death.

Table 20. Distribution of different types of CV death

Cause of CV death	**N (%)**
Myocardial ischaemia and infarction	4 (4.9)
Hyperkalaemia	1 (1.2)
Haemorrhagic pericarditis	1 (1.2)
Other causes of cardiac failure	11 (13.7)
Cardiac arrest / sudden death	21 (25.9)
Hypertensive cardiac failure	1 (1.2)
Hypokalaemia	1 (1.2)
Fluid overload / pulmonary oedema	8 (9.9)
Pulmonary embolus	4 (4.9)
Cerebrovascular accident	25 (31.0)
Mesenteric infarction	4 (4.9)

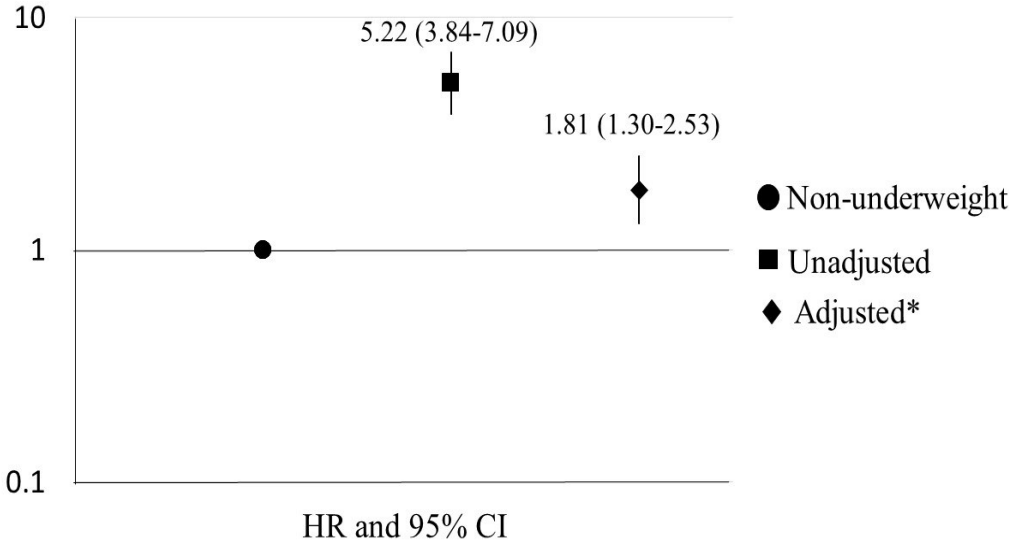
CV-cardiovascular, N-number

3.3.3.1 Association of CVRFs with all-cause mortality

For all analyses log minus log plots were used to check the proportionality assumptions of the Cox proportional hazard models. Only for the association between hypertension with all-cause and CV mortality (Appendix 1 Figures 1 and 2, page 356) the assumption was violated. The log minus log plots indicated for the association with all-cause mortality crossing lines after 2.5 and 6 years follow-up and for the association with CV mortality the lines crossed once after 2.5 years follow-up. Therefore, separate hazard ratios were derived for the association of hypertension with all-cause and CV mortality for these different follow-up periods.

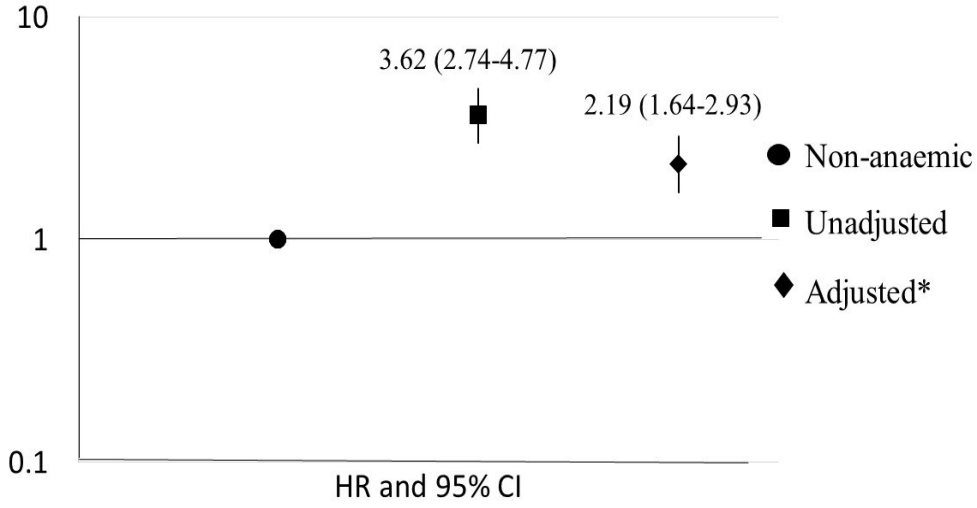
For all the analyses the patients without the CVRF studied are used as reference category. The results of the associations between the individual CVRFs and all-cause mortality are depicted in Figures 18-24. More detailed information about HRs and 95% CIs is included in Appendix 1, Tables 3 and 4, page 357. Underweight/anaemic patients had a higher risk of all-cause mortality compared to non-underweight/non-anaemic patients (Figure 18 and 19, respectively).

Figure 18. Association of underweight with all-cause mortality



*for age, sex, PRD, type and duration of RRT and European region
Non-underweight N=7,125; underweight=321

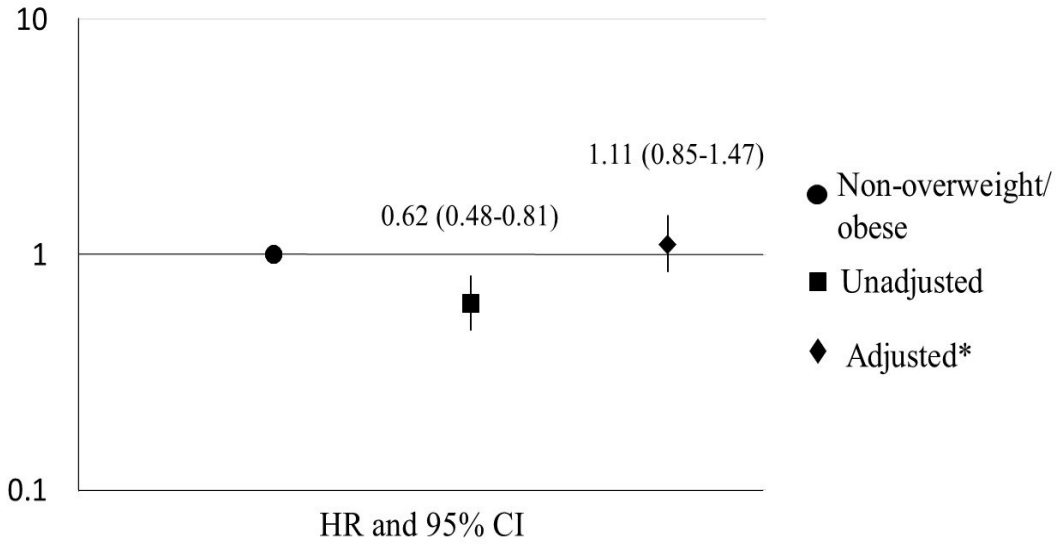
Figure 19. Association of anaemia with all-cause mortality



*for age, sex, PRD, type and duration of RRT and European region
Non-anaemic N=3,649; anaemic N=2,049

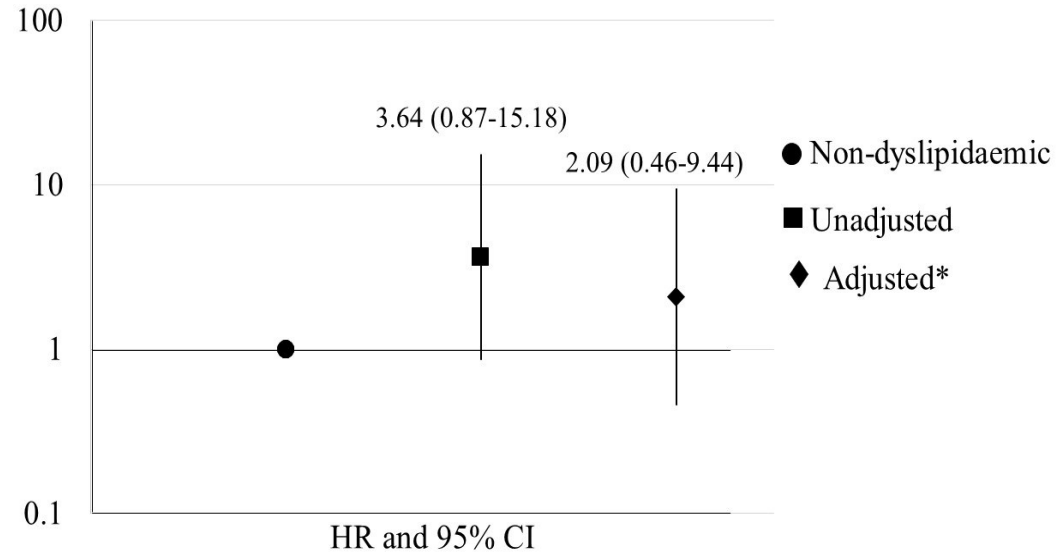
Overweight/obesity (Figure 20), dyslipidaemia (Figure 21) and hypertension (Figure 22, 23 and 24) were positively associated with all-cause mortality. However, the results were not statistically significant.

Figure 20. Association of overweight/obesity with all-cause mortality



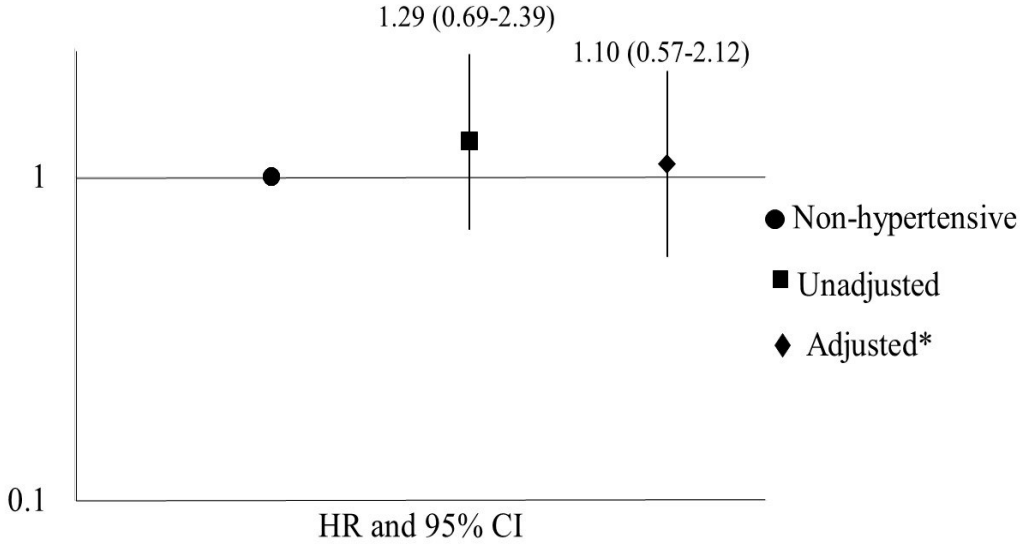
*for age, sex, PRD, type and duration of RRT and European region
Non-overweight/obese N=5,222; Overweight/obese N=2,224

Figure 21. Association of dyslipidaemia with all-cause mortality



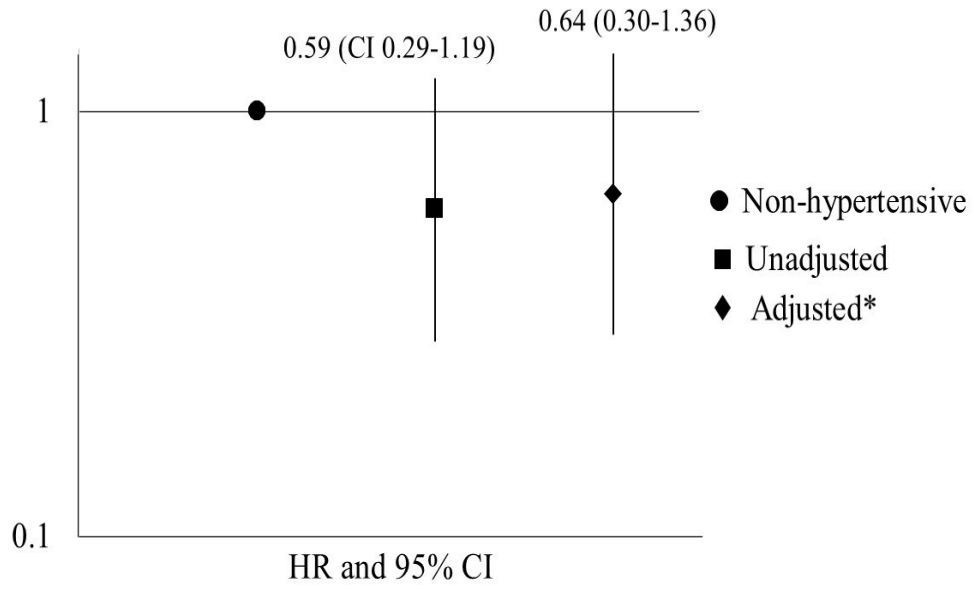
*for age, sex, PRD, type and duration of RRT, European region and overweight/obesity
Non-dyslipidaemic N=204; dyslipidaemic N=1,434

Figure 22. Association of hypertension with all-cause mortality during first 2.5 years of follow-up



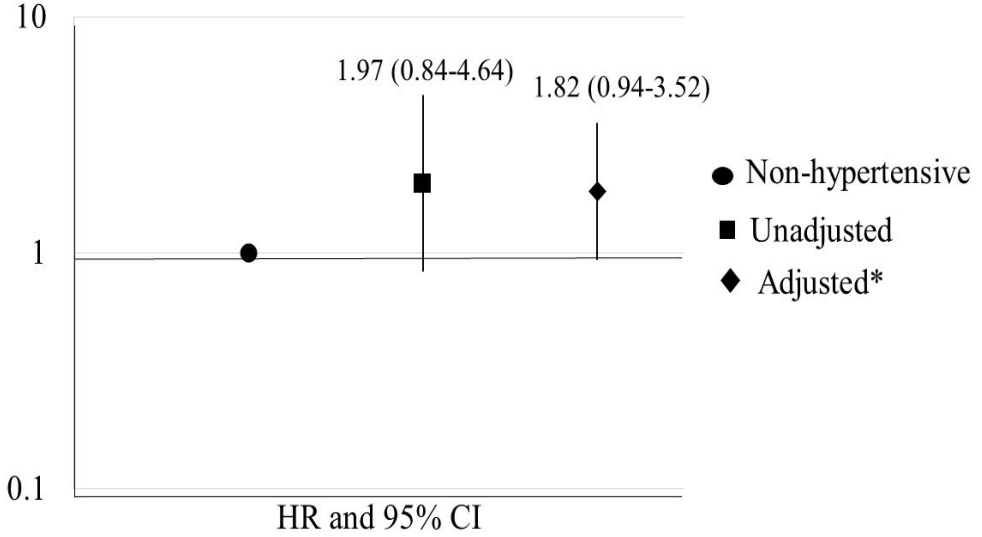
*for age, sex, PRD, type and duration of RRT, European region and overweight/obesity
Non-hypertensive N=1000; hypertensive N=3,840

Figure 23. Association of hypertension with all-cause mortality from 2.5 to 6 years of follow-up



*for age, sex, PRD, type and duration of RRT, European region and overweight/obesity
Non-hypertensive N=1000; hypertensive N=3,840

Figure 24. Association of hypertension with all-cause mortality after 6 years of follow-up

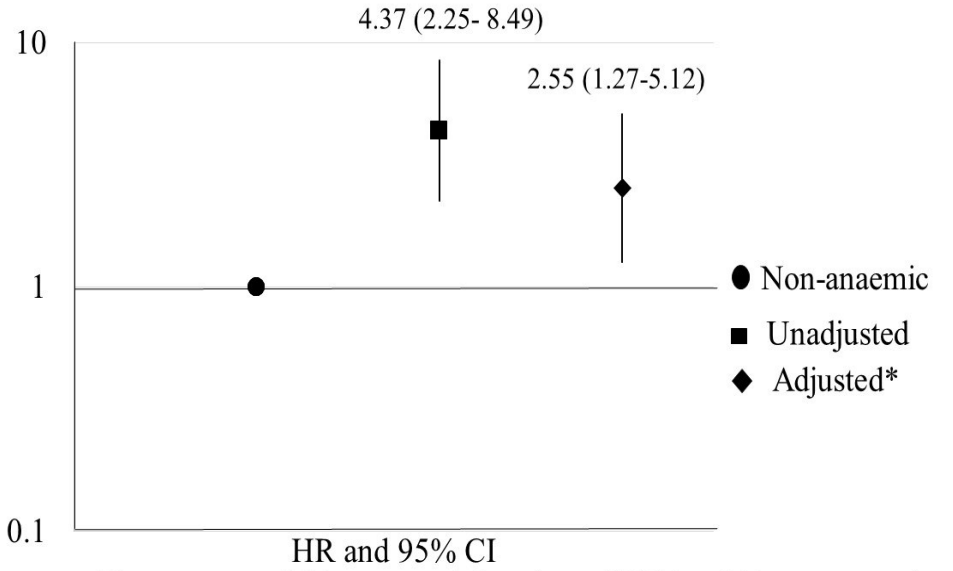


* for age, sex, PRD, type and duration of RRT, European region and overweight/obesity
Non-hypertensive N=1000; hypertensive N=3,840

3.3.3.2 Association of CVRFs with CV mortality

The results of the associations between the individual CVRFs and CV mortality are depicted in Figures 25-29. A statistically significant association was found between anaemia and CV mortality. Anaemic patients had a higher risk of CV mortality compared to non-anaemic patients (Figure 25).

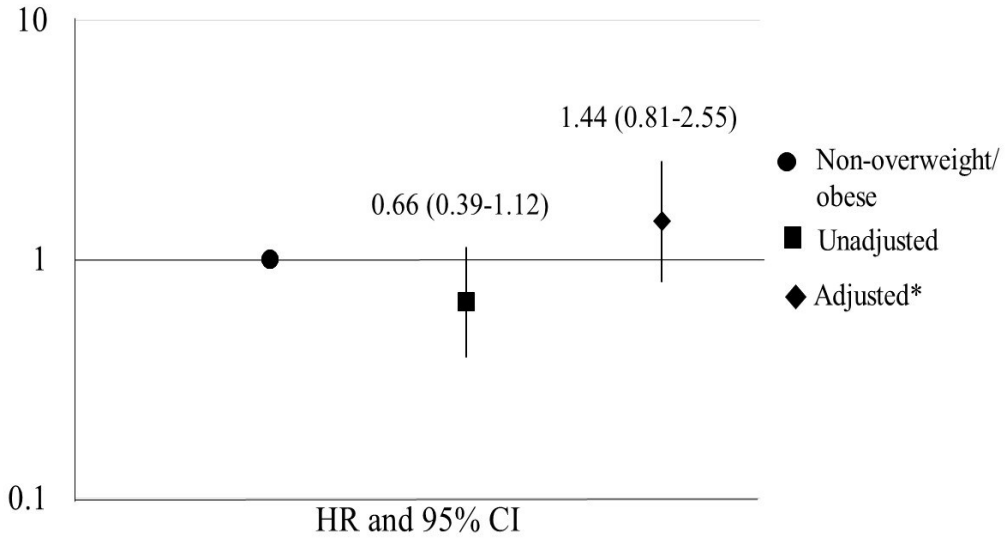
Figure 25. Association of anaemia with CV mortality



*for age, sex, PRD, type and duration of RRT and European region
Non-anaemic N=3,649; anaemic N=2,049

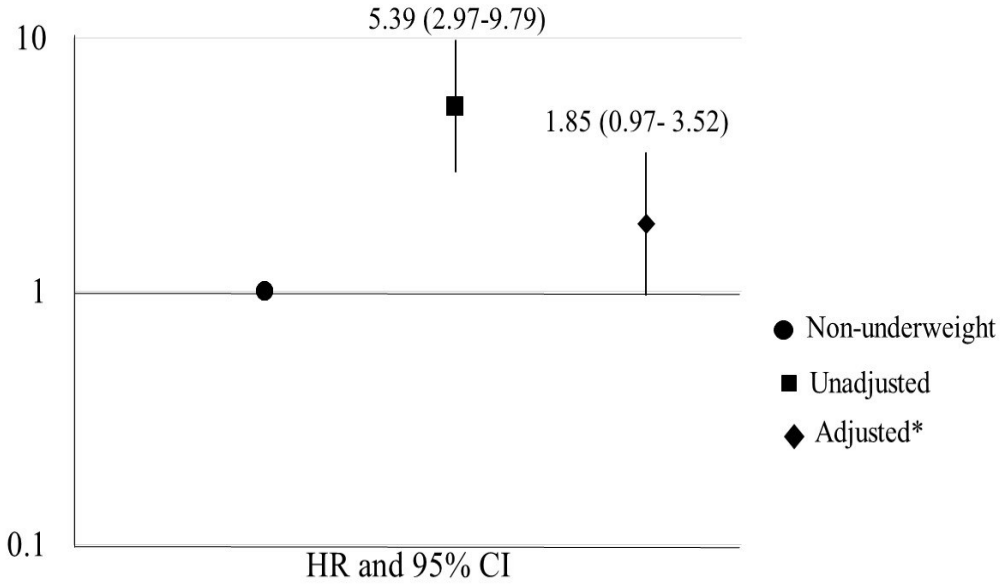
The associations between overweight/obesity (Figure 26), underweight (Figure 27) and hypertension (Figure 28 and 29) with CV mortality were not statistically significant. Since there were no CV deaths in the non-dyslipidaemic group it was not possible to perform Cox proportional hazards analysis to determine the association between dyslipidaemia and CV mortality.

Figure 26. Association of overweight/obesity with CV mortality



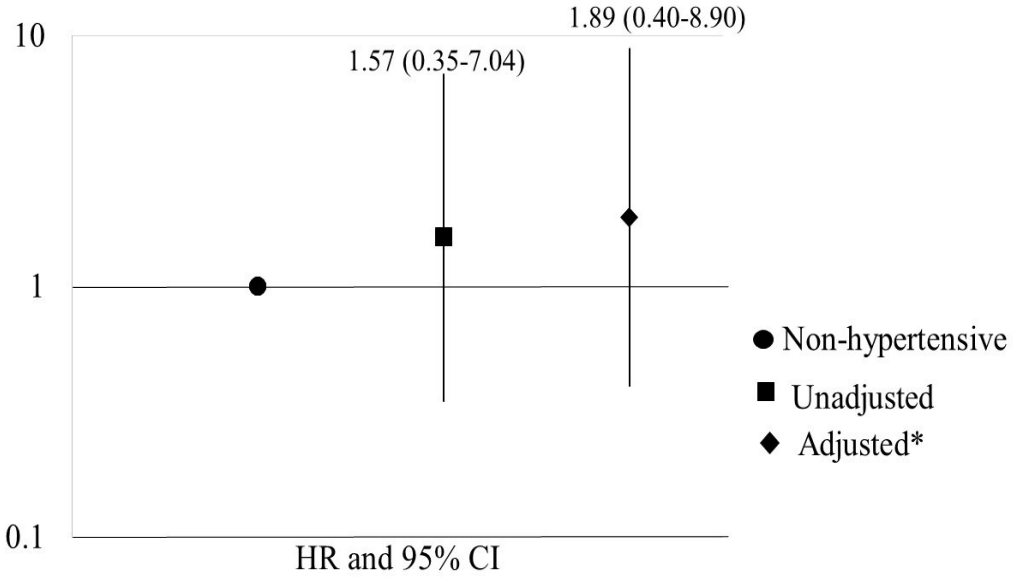
*for age, sex, PRD, type and duration of RRT and European region
Non-overweight/obese N=5,222; Overweight/obese N=2,224

Figure 27. Association of underweight with CV mortality



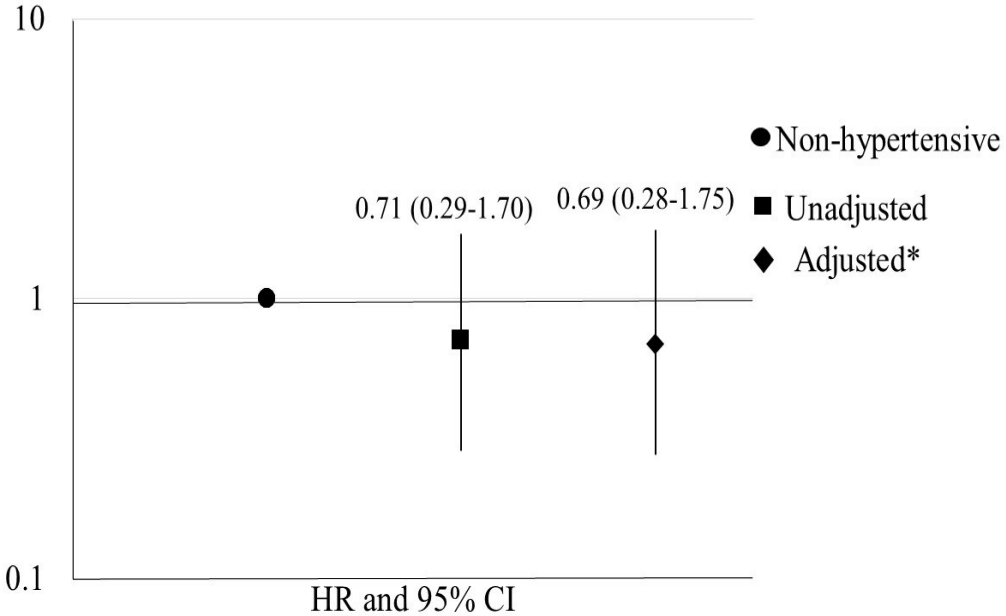
*for age, sex, PRD, type and duration of RRT and European region
Non-underweight N=7,125; underweight=321

Figure 28. Association of hypertension with CV mortality during first 2.5 years of follow-up



*for age, sex, PRD, type and duration of RRT, European region and overweight/obesity
Non-hypertensive N=1000; hypertensive N=3,840

Figure 29. Association of hypertension with CV mortality after 2.5 years of follow-up



*for age, sex, PRD, type and duration of RRT, European region and overweight/obesity
Non-hypertensive N=1000; hypertensive N=3,840

In summary, the results show that among the four CVRFs underweight and anaemia were statistically significantly associated with higher risk of all-cause mortality. Only anaemia showed a statistically significant association with CV mortality.

3.3.4 Planned sensitivity analysis

The exclusion of CVRFs measurements taken in the last six months before death resulted in the exclusion of 84 patients, of which 23 deaths were due to a CV cause. There was no difference with regard to the baseline characteristics of the total cohort before and after exclusion (Table 21). The sensitivity analyses focusing on the prevalence of the CVRFs showed that the overall prevalence of CVRFs remained similar to the primary analysis (Appendix 1 Table 5, page 359). The survival analysis excluding CVRFs measurements taken in the last six months before death showed similar findings to the primary survival analysis (Appendix 1 Table 6 and 7, page 360). The HRs and their accompanying CIs of the associations between dyslipidaemia and all-cause mortality (unadjusted and adjusted) and hypertension with CV mortality (adjusted), were twice as high as those obtained in the primary analysis. However, also these results were not statistically significant.

Table 21. Characteristics of cohort used for primary and sensitivity analyses

Characteristics	**Primary analysis N=7,845 n (%)**	**Sensitivity analysis N=7,761 n (%)**
Age at start of RRT (years)		
0-<2	1,210 (15.4)	1,167 (15.0)
2-<6	1,205 (15.4)	1,187 (15.3)
6-<12	2,300 (29.3)	2,292 (29.5)
12-20	3,123 (39.8)	3,108 (40.1)
missing	7 (0.1)	7 (0.1)
Sex		
Male	4,617 (58.9)	4,571 (58.9)
Initial type of RRT		
HD	2,775 (35.4)	2,742 (35.3)
PD	3,518 (44.8)	3,474 (44.8)
Tx	1,359 (17.3)	1,354 (17.4)
Unknown/missing	193 (2.5)	191 (2.5)
PRD		
CAKUT	3,202 (40.8)	3,184 (41.0)
GN	1,237 (15.8)	1,221 (15.7)
Cystic Kidney Disease	787 (10.0)	779 (10.0)
Hereditary Nephropathy	594 (7.6)	584 (7.5)
Ischaemic Renal Failure	137 (1.7)	135 (1.7)
HUS	314 (4.0)	310 (4.0)
Metabolic Disorders	273 (3.5)	270 (3.5)
Vasculitis	171 (2.2)	169 (2.3)
Miscellaneous	578 (7.4)	565 (7.3)
Unknown/missing	552 (7.0)	544 (7.0)

RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis; Tx, renal transplant; PRD-primary renal disease, GN-glomerulonephritis, CAKUT, congenital anomalies of the kidney and urinary tract; HUS, haemolytic-uremic syndrome.

3.4 Discussion of the ESPN/ERA-EDTA registry analyses

3.4.1 Summary of findings of the study

Prevalence and patterns of CVRFs

The current analyses show that dyslipidaemia, hypertension, anaemia and overweight/obesity are common among young European RRT patients. The prevalence of CVRFs varied significantly by age, type of RRT and European region. Dyslipidaemia, anaemia and underweight were more common among younger patients compared to older ones, while older patients were more frequently hypertensive and overweight/obese compared to younger patients. Almost all CVRFs were more prevalent among patients receiving dialysis, compared to transplanted patients. However, overweight/obesity was more common among patients after kidney transplantation. Patients from Eastern Europe had the highest prevalence of all CVRFs apart from overweight/obesity that was more common in Western and Northern regions. The analyses of the combinations of CVRFs showed that the most frequent combination of CVRFs among dialysis patients was dyslipidemia, hypertension and anaemia and among transplanted children was dyslipidemia, hypertension and overweight/obesity.

Cause of death and the association of CVRFs with outcomes

This study has found that CVD and infections were the most common causes of death in patients under 20 years of age receiving RRT. The most common CV causes of death were cerebrovascular accident and cardiac arrest. The survival analyses showed statistically significant associations between underweight and all-cause mortality and for anaemia with all-cause and CV mortality. These findings persisted even when

measurements taken in the last six months of life were excluded suggesting that they are not entirely explained by reverse causality. Dyslipidaemia, hypertension and overweight/obesity were positively associated with all-cause mortality; however, the results were not statistically significant. Similarly, hypertension, overweight/obesity and underweight were positively associated with CV mortality, but not statistically significant.

3.4.2 Interpretation of the findings in the context of existing literature

3.4.2.1 Prevalence and patterns of CVRFs

Comparison with general pediatric populations

The prevalence of CVRFs appears to be higher in young RRT patients compared to estimates from European paediatric general populations. The overall prevalence of hypertension in the current study was 79.3%, while it is only 10.5% and 12.4% in the general paediatric population of boys and girls in Switzerland, respectively (137). For dyslipidaemia the current study reported an overall prevalence of 87.5% that is higher that figures reported in the German general paediatric population. In Germany the prevalence of different dyslipidaemia measurements ranged from 18%-27% (138). Similarly, the overall prevalence of overweight/obesity of 29.9% found in this analysis was higher than the prevalence of obesity and overweight of 7% and 12.8% reported in a study including children from the general population (139). The overall prevalence of anaemia in the current study was 36.0%, while it is 9.4% in the general population of children from 11 European countries (140).

Comparison with other paediatric RRT populations

Anaemia

The prevalence of anaemia was 50.5% and 21.2% among dialysis and transplanted patients in the current study. The failing kidneys that cannot secrete the hormone erythropoietin (EPO) can explain the higher prevalence of anaemia among dialysis patients. This hormone is a necessary stimulus for normal bone marrow to produce red blood cells (141). Low EPO levels cause red blood cell count to drop and anemia to develop. In transplanted patients anaemia is attributed to immunosuppression therapy used post-transplantation combined with other contributing factors such as viral infection. Immunosupression therapy is associated with generalised bone marrow suppression involving all cell lines (142). Besides immunosupression therapy cytomegalovirus and human herpesvirus infections have also been associated with anaemia in renal transplant recipients (142).

The prevalence of anaemia in dialysis patients (50.5%) found in this analysis was lower compared to the NAPRTCS registry of 67.8% (71). This might be partly explained by the fact that the authors of the latter study used Ht to define anaemia, while in this study Hb was used. Volume overload is common among dialysis patients. Hb/Ht values are affected by patients fluid status and hypervolaemic patients might have lower Hb/Ht values (73). As a patient's fluid status impacts Ht more than Hb (73), it can in part explain that the NAPRTCS study reported a higher prevalence of anaemia. The prevalence of anaemia among transplanted patients found in this analysis was similar to another study from the US including transplanted patients using the same definition of anaemia (67). The authors reported an anaemia prevalence of 25.5%

at 1 year after transplantation. However, another cross-sectional study from Israel (68) reported a higher prevalence of anaemia among transplanted patients of 38% after an average 5.1 years (SD ±3.4) of follow-up. This might be explained by the use of different definitions. In contrast to our analyses the authors of the last study classified patients who were prescribed EPO as anaemic. This approach might have resulted in overestimation of the prevalence as patients with controlled Hb might be classified as anaemic.

Hypertension

The reported prevalence of hypertension was 82.3% and 77.1% for dialysis and transplanted patients in the current study, respectively. An explanation for higher prevalence of hypertension among dialysis patients compared with transplanted patients might be a decreased residual diuresis that consequently leads to fluid overload. Research has shown that fluid overload is independently associated with higher BP (143). In transplanted patients the high prevalence of hypertension could be explained by the use of corticosteroids, such as prednisone, to prevent rejection of the kidney transplant (144). Mechanisms for steroid-induced hypertension include a direct mineralocorticoid action and stimulation of angiotensin II type I receptors, resulting in increased sodium and fluid retention, and increased cardiac output and total peripheral resistance (144). Other commonly prescribed drugs include EPO, used to manage anemia associated with chronic renal failure. Apart from increasing Hb, EPO increases the sensitivity to endogenous vasopressors, and may have a direct vasopressor effect on the vessels (144).

The estimates of the prevalence in the current study are in line with several other published studies from different population (81, 89, 92). However, one cross-sectional study from the US reported a lower prevalence among dialysis patients of 59% (86). This difference can probably be explained by not including the use of antihypertensive medication in the definition of hypertension.

Dyslipidaemia

This study found a higher prevalence of dyslipidaemia among dialysis patients compared to transplanted patients. This might be explained by glucose absorption from the dialysis fluid in PD patients (145). Studies in adult patients treated with PD reported a correlation between serum lipids and intraperitoneal glucose absorption (102).

According to the literature review, there were no studies describing the prevalence of dyslipidaemia among dialysis population apart from the ESPN/ERA-EDTA study (63). Therefore, it was not possible to compare this results with other studies. Moreover, it was difficult to compare the prevalence of dyslipidaemia in transplanted patients with existing studies. Most of the existing studies reported the prevalence of hypercholesterolemia, excluding the prevalence of hypertriglyceridemia. Therefore, the overall prevalence of dyslipidaemia among transplanted patients reported in the current study of 84.5% was higher compared to the other studies. To illustrate, a single-centre study in Mexico reported the prevalence of hypercholesterolemia of 25%, defined as cholesterol >170 mg/dl, at two years after transplantation (79). A single-centre study conducted in Canada reported the prevalence of hypercholesterolemia of 47% after a mean time of 3.4 years (SD 2.8) post-transplantation (90).

Overweight/obesity

The reported prevalence of overweight/obesity in the current study was 20.6% and 40.6% for dialysis and transplanted patients, respectively. The finding that overweight/obesity was more common among patients after kidney transplantation might be explained by the use of corticosteroids. It was shown that corticosteroids are associated with post-transplant weight gain (77). This analysis also showed that overweight/obesity was more common among older patients compared to younger ones, and this is at least partly explained by the larger proportion of transplanted patients among older compared to younger patients. Analysis of type of RRT stratified by age are presented in the Appendix 1, Figure 3, page 364.

The estimates of this study were higher compared with several other published studies from different population. For example, the USRDS registry reported that the prevalence of obesity, defined as BMI $\geq 95^{th}$ percentile for age and sex, among HD patients was 11% (81). Post-transplant prevalence of obesity in two US studies was 31%-36% in the period between 3 to 36 months post-transplantation (78) and 29% at 1 year post-transplantation (77). The difference may in part be explained by the combined definition of overweight and obesity resulting in a higher prevalence. There were no studies describing the prevalence of underweight among patients <20 years of age receiving RRT apart from the ESPN/ERA-EDTA study (37) and, therefore, it is not possible to compare the current results with other studies.

Prevalence stratified by European region

The analysis of the prevalence of CVRFs by European region showed that the prevalence of hypertension, dyslipidaemia, anaemia and underweight was the highest in Eastern Europe. However, overweight/obesity was more prevalent among Western

and Northern Europe. This might be explained by differences in the distribution of RRT modalities with most transplanted patients in Western and Northern Europe and the proportion of dialysis patients highest in Eastern Europe (Appendix 1, Table 8, page 365). This difference might be explained by disparities in public health expenditure and access to kidney transplantation. Recent ESPN/ERA-EDTA study showed that eastern Europe had the highest risk of mortality due to restricted public health financing compared with wealthier northern, southern and western European countries (146).

Combinations of CVRFs

Among dialysis patients the most common combination of CVRFs is dyslipidemia, hypertension and anaemia. This might be explained by the high risk of fluid overload which is associated with higher BP levels and haemodilution (143), resulting in lower Hb values (73). Moreover, tissue hypoxia caused by anaemia leads to vasodilation, which triggers the activation of sympathetic nervous system and arterial stiffness, eventually leading to hypertension (147). A large proportion of transplanted patients have a combination of dyslipidemia, hypertension and overweight/obesity. A possible explanation is the high prevalence of overweight/obesity among transplanted patients. Previous studies in the general paediatric population showed that CVRFs are more prevalent in obese than non-obese children. For example, Freedman et al. reported that obese children have a higher risk of elevated BP, LDL cholesterol, and TG, low HDL cholesterol, and high fasting insulin concentration (148).

The most common combination of CVRFs (dyslipidemia, hypertension and anaemia) in dialysis patients was not possible to compare to other studies as no studies reported this information. However, the most common combination of CVRFs (dyslipidemia,

hypertension and overweight/obesity) among transplanted children is in line with the study conducted by Ramirez-Cortes et al. (79). The authors showed that transplanted children who were obese are more likely to suffer from MeS compared to non-obese children. MeS was defined as the presence of three or more of the following risk factors: hypertension, glucose intolerance, low HDL cholesterol, hypertriglyceridemia and overweight (79).

3.4.2.2 Cause of death

In this study, CVD was the most common cause of mortality in patients under 20 years of age receiving RRT (22.7%) with the most common types of CVD being cerebrovascular disease and cardiac arrest. This finding corresponds with a study conducted by the USRDS registry including patients from 0 to 30 years of age receiving RRT (149). The authors reported that CV mortality accounted for 22.5% of all deaths and cardiac arrest was the most common cause of CV death.

However, two other studies reported a two times higher proportion of CV deaths compared to the current study. For example, the study from the Dutch Renal Registry and the ANZDATA registry showed that CVD accounted for 41% and 45% of all deaths, respectively (28, 53). The proportion of CV death in both studies was higher presumably due to the longer follow-up time. The follow up of the current study was 3.7 years (IQR 1.7-6.8) while the Dutch and ANZDATA studies followed their patients over the mean of 15.5 years (SD not reported) and median of 9.7 years (IQR not reported), respectively. As CV death is more likely to occur later in life after a longer follow-up time, both studies might have reported more CV deaths compared to the current study

3.4.2.3 The association of CVRFs with outcomes

The survival analyses showed that anaemic patients had a statistically significantly higher risk of all-cause mortality compared to non-anaemic patients. This finding was in line with two previous studies conducted in dialysis populations that were discussed in details in the systematic review. Briefly, the NAPRTCS registry reported that patients with anaemia had an estimated 52% greater risk of death than non-anaemic patients (71). The IPPN registry showed that the risk of all-cause mortality was independently inversely associated with Hb, adjusted HR of 0.23 per g/dl of Hb (95% CI not reported) after a median follow-up of 0.8 year (IQR, 0.22-1.56 years) (22).

The current study also showed that anaemic patients had a higher risk of CV death compared to non-anaemic patients. This is the first study investigating this association thus it is not possible to compare these findings with previous studies. However, the findings from the current study correspond to studies including adult RRT population. For example, a US study including Medicare incident HD patients showed that higher Ht values were associated with lower risk of CV morbidity and CV mortality over three years follow up (150).

Results of the current study showed no significant associations between overweight/obesity and all-cause and CV mortality which is in line with earlier published results from the NAPRTCS study (see for details also the systematic review) (54). However, the NAPRTCS study showed increased mortality in obese 6 to 12 year old children compared to age matched non-obese children. However, it needs to be mentioned that this might be a chance finding due to multiple testing.

This study has found that underweight patients had a significantly higher risk of all-cause mortality compared to non-underweight patients. This finding corresponds to another study from the USRDS registry including patients receiving RRT (107) discussed in my systematic review. The authors reported a U-shaped association between BMI and risk for all-cause mortality (107).

This study did not find statistically significant associations between hypertension and all-cause and CV mortality. However, the Dutch Renal registry study included in the systematic review (29) showed different results. The authors showed that hypertensive patients had a threefold higher rate of all-cause mortality and a more than two times higher risk for cerebrovascular death compared to non-hypertensive patients after the mean follow-up of 15.5 years. This difference might be explained by the inclusion of older RRT population with longer follow-up in the Dutch study, which allowed the latter study to capture more outcome events compared to the current study.

Similarly, I did not find an association between dyslipidaemia and all-cause mortality. There are no studies describing the association of dyslipidaemia with all-cause and CV mortality in children receiving RRT, so it was not possible to compare current findings with previous studies. However, it was shown previously that in the general paediatric population dyslipidaemia persists into adulthood and predicts CVD in later life (151).

3.4.3 Limitations of the study

This study had several limitations that should be mentioned and taken into account interpreting the results of the study.

3.4.3.1 Missing data and selection bias

Almost all participating countries in the ESPN/ERA-EDTA registry were included in the current study. However, due to the fact that some registries have only quite recently started their data collection, the number of patients were very low for some countries. The results are weighted quite heavily by data from the countries which contributed the majority of the data (UK, Russia, Italy, France, Spain, Switzerland). I have accounted for the fact that different European countries will be represented to different degrees by stratifying the prevalence and adjusting the survival analysis for different European regions. However, the results of this study will be mostly representative for the countries which were overrepresented in the current study. It might be that countries with a better healthcare system will have more complete data on CVRFs and causes of death, therefore, the results of these analyses would be biased towards wealthier countries.

Countries with missing CVRFs data were excluded from the analyses. Most of the missing data was on lipids measurements, while other CVRFs measurements such as BMI, Hb and BP levels were provided by the majority of countries. The proportion of transplanted patients was higher in patients with available BP and Hb compared to patients with missing data on these CVRFs. This might be because transplanted patients require immunosuppressive medication that has adverse effects in terms of high BP and low Hb level, therefore, need more frequent monitoring. As the prevalence of hypertension and anaemia is lower among transplanted population inclusion of larger proportion of transplanted patients might have resulted in underestimation of the true prevalence of these CVRFs. Moreover, survival of transplanted patients is higher compared to dialysis population. Therefore, the

associations of hypertension and anaemia with all-cause and CV mortality might also have been underestimated.

In contrast, the proportion of patients receiving dialysis was higher among patients with available BMI measurements compared to patients with missing data. This might be because patients receiving dialysis require frequent BMI measurements to control dialysis regime to achieve a dry body weight. Patients on dialysis are more frequently underweight (152) and less overweight. Therefore, this might have led to overestimation of the proportion of underweight patients, but underestimation of the prevalence of overweight/obesity. Moreover, dialysis patients have a higher risk of death compared to transplanted patients. It might have affected the obtained HRs for the associations of underweight with all-cause and CV mortality towards overestimation.

For the analysis of multiple CVRFs I could only analyse a limited number of patients. When comparing the included patients with patients with missing data, young patients (0-<2 years old) were overrepresented in the included cohort. Moreover, included patients were less likely to be pre-emptively transplanted and more frequently started on PD, as PD is more common among younger patients. The fact that complete data on all CVRFs was available for the younger children might be explained by the fact that young children have a higher risk of mortality compared to older children (153) and, therefore, require more careful and frequent monitoring. Therefore, the patterns of multiple CVRFs might not be generalisable for the entire RRT population of children in Europe.

Also, there was a high proportion of missing cause of death that were excluded from the analysis of CV mortality. If there were more deaths due to CVD among patients with missing data CV mortality might be underestimated. However, this is unlikely because CV death is expected to be recorded in the death certificates due to awareness of high risk of CVD in this population.

3.4.3.2 Misclassification of patients by exposure and outcome status and residual confounding

Information about specific methods for CVRFs measurements at the participating centres was not available in the registry. In particular, information is lacking with respect to the timing of BP and BMI measurements in dialysis patients. Use of pre-dialysis measurements of BMI and BP might overestimate the prevalence of obesity and hypertension due to the presence of fluid overload (154). In general, the ESPN/ERA-EDTA registry requests pre-dialysis BP readings that possibly partly explains the high prevalence of hypertension in patients on dialysis found in this study. However, the registry requests data on dry body weight, therefore, any overestimation of BMI is likely to be small. This misclassification of patients with and without CVRFs is likely to be non-differential, which tends to bias the association towards the null (155).

Misclassification of all-cause mortality is unlikely because the ESPN/ERA-EDTA registry collects mortality data submitted by the participating national registries. However, there is definitely a risk of misclassification of the cause-specific mortality. It is most likely that the causes of deaths were obtained from death certificates that might have led to misclassification of CV causes of death. Previous studies among the

general adult population have shown that death certificates tend to overestimate CV causes of death compared to deaths that were validated by autopsy (156).

Information about the presence of comorbidities, which can increase the risk of death (157) was not available in the registry. Comorbidities might be important confounding factors in these associations. The IPPN registry reported that out of 1,830 children receiving PD 32.9% of patients had at least one comorbidity. The most common type of comorbidity was cognitive abnormality (15.5%) followed by motor abnormality (12.6%). The authors showed that compared with patients not having a comorbidity, those with any comorbidity had a significantly lower survival rate (73% vs 90%, $p<0.0001$) (157).

3.4.3.3 Limitation of methods used

Due to the lack of baseline measurements of CVRFs (taken at the start of RRT) in the majority of patients, both incident and prevalent RRT patients were included in the current study. This resulted in the inclusion of patients with highly variable duration of RRT, median 2.3 years (IQR 0.5-5.6). To control for this the analysis was adjusted for the period from the start of RRT to the time of first CVRF measurement.

Moreover, I used a simplistic methodological approach to summarise the repeated CVRFs measurements and changes in RRT modality into one derived summary measure. This method may not have sufficiently captured the change in measures over time and the effect this may have had on the outcome. Additionally, the summarised repeated measurements did not allow to classify patients with available BMI measurements into three categories: underweight, normal weight and overweight/obese. This method only allows to categorise patients into two groups:

overweight/obese versus non-overweight/obese and underweight versus non-underweight.

Another limitation related to the methods of the study was that all available CVRFs measurements per patient during follow-up time were included in the primary analysis. This approach was chosen to be able to include as many patients as possible to the study. However, such an approach may mean that CVRFs measurements, measured soon before death, are not predictors of death but are rather markers for the severity of the underlying renal pathology (158). However, a sensitivity analysis excluding patients whose measurements were taken in the last six months before death led to similar results to those obtained in the primary analysis.

Finally, due to the observational nature of the study it is not possible to claim any causal relationships for the factors that were found to be associated with all-cause and CV mortality. Nevertheless, this large scale European study provides important knowledge which will help to optimise CVD management in children receiving RRT.

3.4.4 Strengths of the study

3.4.4.1 Sample size and generalisability of results

This is the first study focusing on CVRFs in young patients receiving RRT. One of the biggest strengths of this study is the use of the European international dataset that allowed to include a large number of patients who initiated RRT in childhood. Furthermore, most European countries participating in the ESPN/ERA-EDTA registry were included in the analysis with all regions of Europe represented in the registry. This shows high generalisability of the obtained results to the European population under 20 years of age receiving RRT. Previous studies are predominantly from the US

(54, 72, 159, 160) or from a single European country (29). The finding of the US studies might be difficult to extrapolate to the European population due to the differences in health care systems and a higher proportion of black people in the US compared to Europe. It has been shown in previous studies in adults with ESRD that black patients have a higher risk of ESRD compared to white patients (161).

Furthermore, this is the first European study including patients with all age groups from 0-20 years of age and both dialysis and transplanted patients. This makes it possible to explore differences in prevalence of CVRFs between sub-groups of patients by age at start of RRT and type of RRT. Furthermore, this makes obtained results generalisable to the entire RRT population of patients from 0-20 years old. In contrast, most of the previous studies discussed in the systematic review included selected population of RRT patients, either on dialysis (72, 160, 162) or after kidney transplantation (54) or certain age groups (72).

3.4.4.2. Follow-up period

Another strength of this study is the relatively long follow-up period when comparing with other available studies. For example considering anaemia this is the study with longest follow-up of 3.7 years (IQR 1.7-6.8) Until now, the association between anaemia and outcome was investigated in the NAPRTCS registry with 2.6 years follow-up available (160).

3.4.4.3 Novel findings

This is the first study using data from the ESPN/ERA-EDTA registry that described several CVRFs, their patterns and regional difference of prevalence of CVRFs. Previous studies only focused on describing the prevalence of single CVRFs.

Additionally, there is the gap in the literature about the association of dyslipidaemia with all-cause mortality. This is the first study that described this association in children receiving RRT.

Most importantly, the access to cause specific mortality records allowed to study the association of CVRFs with CV mortality. This study, therefore, provides an important and novel contribution, since there are no studies describing the association of CVRFs with CV mortality. As shown in my systematic review there was only one study performed by the Dutch Renal Registry (29) that examined the association between hypertension and cerebrovascular disease mortality. However, this study only included a selected RRT population of survivors into adulthood and only reported crude RRs.

3.5 Conclusion and future research

In conclusion, the current study has added novel insights and results to this research field. This study showed that dyslipidaemia, hypertension, anaemia and overweight/obesity are common among young European patients receiving RRT. The prevalence of the majority of CVRFs was lower in transplanted than among dialysis patients. This finding underlines the beneficial effects of transplantation in terms of improved CVRF profile. In addition, the combination of dyslipidemia, hypertension and anaemia was most common in dialysis patient and the combination of dyslipidemia, hypertension and overweight/obesity was most common in transplanted patients. Patients who were underweight/anaemic had a higher risk of all-cause mortality compared to non-underweight/non-anaemic patients. Anaemic patients had a higher risk of CV mortality compared to non-anaemic patients. Future research is needed to clarify whether treatment of anaemia will reduce CVD and death in patients

who initiated RRT in childhood. Detailed discussion about future study designs that could be performed to answer this remaining question are presented in the overall discussion chapter (Chapter 7).

As the ESPN/ERA-EDTA registry was limited in follow-up of patients up to reaching 20 years of age, further research is needed that would follow patients up from childhood into adulthood and look at the longer-term survival. Furthermore, lack of CVD morbidity data within the ESPN/ERA-EDTA registry did not allow to describe CVD incidence in this population. These limitations should be addressed by using registry data with the access to CVD morbidity records. Both main limitation of the ESPN/ERA-EDTA analyses I addressed by using the SRR registry data. The SRR follows patients up from childhood into adulthood and has an opportunity to link individual patient data with the national registry of causes of death and hospital admissions. These advantages allowed me to describe a longer-term survival and CVD incidence in patients who initiated RRT in childhood. The following chapter provides a literature review focusing on longer-term survival, CVD incidence and the association of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality and CVD incidence in patients who initiated RRT in childhood (Chapter 4). This literature review informed my SRR analysis presented in Chapters 5 and 6.

Chapter 4. Survival, all-cause mortality and cardiovascular disease outcomes in patients who initiated renal replacement therapy in childhood; a literature review

4.1 Introduction

ESRD in children is rare but important health problem, often requiring RRT. The ANZDATA registry showed that all-cause mortality rates in patients who started RRT from 0 to 19 years old were 30 times higher compared to an age- and sex-matched general population (118). CVD is one of the most common causes of death in patients who initiated RRT in childhood. Information about long-term survival and CVD incidence in these patients is limited. The systematic review presented in Chapter 2 described the association of CVRFs (anaemia, hypertension, obesity and dyslipidaemia) with all-cause and CV mortality to inform the ESPN/ERA-EDTA analyses. This literature review was performed in conjunction with the SRR analyses to describe the long-term survival and CVD incidence among patients who initiated RRT in childhood. The aims of this literature review were:

1. To identify, synthesise and critically appraise the existing literature about survival/all-cause mortality and CVD incidence of patients who initiated RRT in childhood.

2. To identify, synthesise and critically appraise determinants for all-cause mortality and CVD incidence in patients who initiated RRT in childhood, such as age at initiation of RRT, sex, PRD, type of RRT and period of initiation of RRT. These particular determinants were of interest partly because these were the risk factors that would be investigated within the SRR analyses.

4.2 Methods

4.2.1 Search strategy

Medline and Embase electronic literature databases were searched using a comprehensive search strategy comprised of Medical Subject Heading terms and keywords for paediatric, renal disease, survival, all-cause mortality and CVD outcomes. The search was limited to the last 5 years (from 2011 to 2016) due to time limitations. The search strategy is presented in Appendix 1 page 366. The reference lists of the relevant papers and annual reports of national and international renal registries were also searched to identify relevant papers and information.

4.2.2 Inclusion and exclusion criteria for study identification for this review

4.2.3.1 Inclusion criteria

Types of studies:

RCTs and observational studies that report survival and/or CVD incidence, and/or association of age at start of RRT, sex, PRD, type of RRT and period of initiation of RRT with all-cause and/or CVD incidence of children with ESRD or patients who initiated RRT in childhood were included.

Types of participants:

Children receiving RRT or patients with childhood-onset RRT.

Types of exposure:

Among studies reporting on determinants associated with all-cause mortality/CVD incidence, exposures of interest were age at start of RRT, sex, PRD, type of RRT and period of initiation of RRT.

Types of outcome:

1. All-cause mortality

2. CVD outcome: fatal and non-fatal CVD events (coronary artery disease, cardiomyopathy, cardiac arrest, valvular heart disease, arrhythmia, cerebrovascular disease, peripheral vascular disease).

4.2.3.2 Exclusion criteria

Studies that report survival and/or CVD outcomes and/or association of age at start of RRT, sex, PRD, type of RRT and period of initiation of RRT with all-cause and/or CVD incidence in patients with adult-onset RRT were excluded.

Studies that reported CV surrogate end-points obtained from non-invasive imaging techniques, such as left ventricular hypertrophy, carotid intima-media thickness, coronary artery calcification or coronary intravascular ultrasound plaque volume were excluded.

4.2.3 Data extraction and assessment of risk of bias and confounding

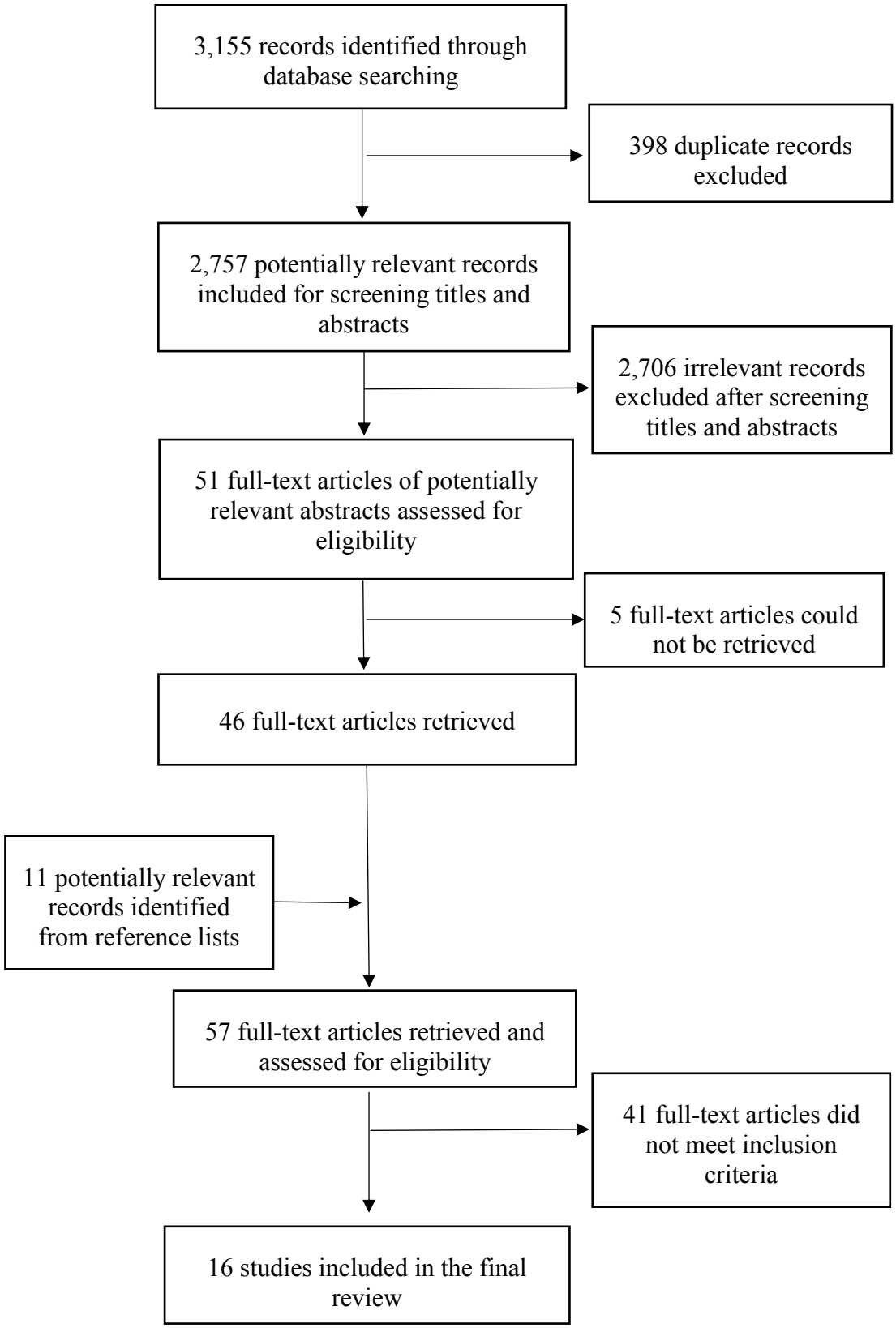
I screened the results of the search strategy to identify relevant studies for inclusion, first by title and abstract and then by full text. Data from relevant full-text studies were extracted: author/s; year of publication; data sources and settings; study population; length of follow-up; categorisation of exposure; incident/prevalent RRT population;

statistical techniques used; and results of the study analysis (crude/adjusted effect estimates and confidence intervals). Results are presented in tables and forest plots. The results were summarised in a narrative synthesis.

4.3 Results

The flow diagram of included and excluded studies is presented in Figure 30. In total, after excluding duplicate records, 2,757 records were identified through two database searches. After screening titles and abstracts 2,706 records were excluded, leaving 51 relevant papers for full-text review. Additional 11 papers were identified from the reference lists. Ultimately, 57 full-text articles were retrieved and assessed for eligibility. Sixteen studies were included in the final literature review.

Figure 30. Flow diagram of included studies in the literature review of survival, CVD outcomes and the associations of age at initiation of RRT, sex, PRD, type of RRT and period of initiation of RRT with all-cause mortality and CVD outcomes



4.3.1 Characteristics of included studies describing survival/all-cause mortality and CVD outcomes in patients who initiated RRT in childhood

Table 22 presents characteristics of the included studies (number in superscript refers to the study identifier). All studies were observational cohort studies. Almost all studies used data from national or multi-national renal registries, apart from one single hospital study from Canada (109). Multi-centre studies were from the USRDS (120, 149, 163, 164), the ESPN/ERA-EDTA (30, 31), the National Dutch Registry of patients on RRT (29, 165), the Canadian Paediatric ESRD registry (14, 110), the ERA-EDTA (166), the ANZDATA (118), the NAPRTCS (167), the UK renal registry (168) and one study combined data from the ESPN/ERA-EDTA, IPPN and ANZDATA registries (169). Sample size ranged from 87 to 23,401 participants. Studies generally included children aged up to 18 years of age at initiation of RRT, while three studies included patients up to two years of age (14, 167, 169) and two studies included children and young adults after reaching at least 18 years of age (120, 149). There was a larger proportion of males than females across all studies. Six studies reported race/ethnicity distribution showing that the proportion of white patients was higher in all studies compared to patients of other race/ethnicity groups. CAKUT and GN were the most common types of underlying ESRD almost in all studies. Studies were heterogeneous in terms of the RRT population. Ten studies included both dialysis and transplanted ESRD populations, while five studies were limited to children/young adults receiving dialysis and one study was limited to a transplanted population. The majority of studies included incident RRT populations. Not all studies reported median follow-up period. Among the 10 studies with reported follow-up, it ranged from 1.2 to 25.5 years.

Table 22. Characteristics of included studies describing survival, all-cause mortality and CVD outcomes in patients who initiated RRT in childhood, presented in chronological order of publication

Author (year)	**Data source**	**Population**	**N**	**Age at the time of the study (range unless stated) ***	**Male %**	**Race/ ethnicity %**	**Distribution of PRD %**	**RRT type**	**Incident/ prevalent patients**	**Follow-up time (total person years unless specified)**
Wong et al. (2001)[163]	USRDS registry	All Medicare/ Medicaid ESRD patients	1,723	0-18 Mean NR	54.8	NR	CAKUT 48.4 GN 26.5 Vasculitis 10.9 Nephrotoxic/tumor related 1.1 Other 6.0 Unknown 7.1	HD PD	Incident	2,953
Chavers et al. (2002)[164]	USRDS registry	All Medicare/ Medicaid ESRD patients	1,454	0-19	54.8	White 58.7 Black 32.2 Other 9.1	GN 47.2 Structural 25.5 Hypertension 7.4 Other 19.9	HD PD	Incident	NR
Groothoff et al. (2002)[29]	National Dutch Registry of patients on RRT, The Netherlands	National	249	Mean 10.6 (range 1.9-14.9)	55.0	NR	NR	HD PD Tx	Incident with survival to adulthood	Average 15.5 years

Author (year)	Data source	Population	N	Age at the time of the study (range unless stated) *	Male %	Race/ ethnicity %	Distribution of PRD %	RRT type	Incident/ prevalent patients	Follow-up time (total person years unless specified)
Parekh et al. (2002)[149]	USRDS registry	All Medicare/ Medicaid ESRD patients	1,380	0-30	54.0	White 69.5 Black 30.5	GN 27.6 Other 72.4	HD PD Tx	Prevalent	NR
McDonald et al. (2004)[118]	ANZDATA registry, Australia and New Zealand	National	1,634	0-19 Mean NR	56.0	NR	NR	PD HD Tx	Incident	Median 9.7 years (IQR 4.1-17.6)
Koshy et al. (2009)[109]	Toronto, Canada Sick Kids Hospital	All paediatric renal transplant patients	274	Mean 10.2 (SD 5.0)	62.8	NR	CAKUT 49.6 Other NR	Tx	Incident	Mean 6.4 years (SD 5.1)
Kramer et al. (2009)[166]	ERA-EDTA registry	98% coverage	1,777	0-18 Mean NR	59.2	NR	Pyelonephritis 26.5 GN 18.1 Hypoplasia/dysplasia 10.0 Cystic kidney disease 8.8 Hereditary nephropathy 7.9 FSGS 6.2	HD PD Tx	Incident with survival to adulthood	NR

Author (year)	Data source	Population	N	Age at the time of the study (range unless stated) *	Male %	Race/ ethnicity %	Distribution of PRD %	RRT type	Incident/ prevalent patients	Follow-up time (total person years unless specified)
							HUS 2.3 Miscellaneous 10.2 Unknown 10.0			
Alexander et al. (2011)[14]	Canadian Paediatric ESRD registry	National	87	0-2 Mean NR	69.0	White 63.2 Aboriginal 10.4 Unknown 26.4	Renal malformation 54.0 Cystic kidney disease 10.3 CNS 8.0 Acute tubular necrosis 3.4 Other/unknown 24.3	PD HD Tx	Incident	Median 4.7 years (IQR 1.4-9.8)
Samuel et al. (2011)[110]	Canadian Paediatric ESRD registry	National	843	Mean 11.3 (SD 5.4)	52.4	NR	CAKUT 28.7 GN 28.9 Genetic 13.3 Other/unknown 29.1	PD HD Tx	Incident	Median 6.8 years (IQR 3.00-10.62)
Van Stralen et al. (2012)[169]	ESPN/ ERA-EDTA, IPPN, ANZDATA	98% coverage	264	0-31 days	64.8	NR	CAKUT 54.6 Cystic kidney disease 13.3 Cortical necrosis 11.4 Renal vascular disease 3.4	HD PD Tx	Incident	Median 28.6 (IQR 11-60) months

Author (year)	Data source	Population	N	Age at the time of the study (range unless stated) *	Male %	Race/ ethnicity %	Distribution of PRD %	RRT type	Incident/ prevalent patients	Follow-up time (total person years unless specified)
							CNS 5.7 HUS 1.1 Oxalosis 0.7 Other 9.8			
Mitsnefes et al. (2013)[120]	USRDS registry	All Medicare/ Medicaid ESRD patients	23,401	0-21 Mean NR	54.4	White 65.8 Black 25.3 Other 8.9	CAKUT 17.9 GN 29.6 FSGS 14.9 Other 18.0 Unknown 17.6 Missing 2.0	HD PD	Incident	65,935
Pruthi et al. (2013)[168]	UK renal registry	National	1,551	0-16	60.4	White 74.5 South Asian 14.1 Black 4.1	Renal dysplasia 32.3 Obstructive uropathy 17.9 GN 13.8 CNS 9.7 Other 26.3	HD PD Tx	Incident	Median 3.4 years (range 1 day-15 years)
Vogelzang et al. (2013)[165]	National Dutch Registry of patients on RRT, The Netherlands	National	249	Median 11.2 (range 1.9-15.0)	54.6	NR	NR	HD PD Tx	Incident with survival to adulthood	Median 25.5 years (IQR 0.3-39.9)

Author (year)	Data source	Population	N	Age at the time of the study (range unless stated) *	Male %	Race/ ethnicity %	Distribution of PRD %	RRT type	Incident/ prevalent patients	Follow-up time (total person years unless specified)
Chesnaye et al. (2014)[31]	ESPN/ERA-EDTA registry; 37 European countries	98% coverage	1,697	0-19 Mean NR	NR	NR	CAKUT 41.3 Other NR	PD HD Tx	Incident	Median 2.2 years (IQR NR)
Chesnaye et al. (2016)[30]	ESPN/ERA-EDTA registry; 37 European countries	98% coverage	6,473	0-18 Mean NR	56.1	NR	CAKUT 32.4 GN 18.3 Cystic kidney disease 9.3 Hereditary nephropathies 7.3 Other/unknown 32.7	HD PD	Incident	10,910
Carey et al. (2016)[167]	NAPRTCS registry	NR	193	0-2 Mean NR	65.2	White 60.5 Black 16.4 Hispanic 17.4 Other 5.7	Renal dysplasia 25.5 Obstructive uropathy 15.8 ARPKD 7.9 CNS 10.8 Other 40.0	HD PD	Incident	Median 14.6 (IQR NR) months

N=total population, PRD-primary renal disease, NAPRTCS- North American Pediatric Renal Transplant Cooperative Study, ANZDATA-Australia and New Zealand dialysis and transplant registry, USRDS-United States Renal data system, IPPN- International Pediatric Peritoneal Dialysis Network, GN-glomerulonephritis, FSGS-focal segmental glomerulosclerosis, CAKUT-congenital anomalies of the kidney and urinary tract, CNS- congenital nephrotic syndrome, ARPKD-autosomal recessive polycystic kidney disease, HUS-haemolytic-uremic syndrome, PD-peritoneal dialysis, HD-haemodialysis, Tx-transplanted patients, SD-standard deviation, IQR-interquartile range, p/y- person years. *Age is presented in years unless otherwise specified. NR-not reported

4.3.2 Mortality/long-term survival and CVD occurrence in patients who initiated RRT in childhood

4.3.2.1 All-cause mortality rate/survival in patients who initiated RRT in childhood

This section summarises the results of all-cause mortality rates and/or survival reported by the included studies. Ten studies described all-cause mortality rates and/or described survival in patients who initiated RRT in childhood (Table 23). Studies in Table 23 are organised based on RRT population and age at initiation of RRT. The overall crude all-cause mortality rate among dialysis populations ranged from 2.8 to 9.8 per 100 p/y. Crude all-cause mortality rates among studies that included both dialysis and transplanted patients ranged from 1.6 to 4.7 per 100 p/y. Most studies reported on a 5-year or shorter follow-up period. One- and five- year survival ranged from 79.8% to 99.4% and from 74.9% to 96.3% across all studies, respectively. Only three studies reported very long-term follow-up. The ANZDATA registry (118), Canadian Paediatric ESRD registry (110) and Dutch Renal registry (29) reported 10-year survival ranging from 78.0% to 85.8%. Twenty-year survival of 66.0% (95% CI 63-69%) was reported by the ANZDATA registry (118), while the Dutch registry (29) reported a higher 20-year survival of 78.0% (95% CI not reported). It was not possible to assess whether this difference is statistically significant due to the lack of 95% CI in the Dutch study.

Patients in the youngest age groups showed the highest mortality rates/lowest survival. For example, the USRDS study reported a mortality rate of 9.8 per 100 p/y (120) in the youngest age strata of patients <5 years of age. The Canadian Paediatric ESRD

registry (14) reported the lowest one- and five-year survival of 79.8% (95% CI 71.6-88.8%) and 74.9% (95% CI 66.1-84.8%), respectively. The high mortality rate/low survival among the youngest patients might be explained by delayed transplantation until the child weighs 10 kg or is two years old. The primary reason for this delay is that renal transplantation is technically difficult in children <2 years old due to the small size of the child compared with the relatively large (usually adult) donor kidney and the small blood vessel calibre of the recipient (14).

The lowest mortality rate of 1.6 per 100 p/y was reported by the Dutch registry (29). The study was limited to patients who initiated RRT in childhood and survived into adulthood by the time of the study initiation. Included patients may be healthier compared to those who did not survive until adulthood, therefore, the lower mortality rates in this study compared to other studies is likely to reflect survival bias.

Longer-term survival (10- and 20-year) was reported by the ANZDATA, Canadian and Dutch renal registries studies (29, 110, 118). The lowest 10- and 20-year survival was reported by the ANZDATA registry (118) presumably due to the inclusion of patients who started RRT in earlier periods (from 1963 onwards) compared to the Canadian (110) and Dutch (29) registries which started in 1972 and 1992, respectively. Improvement in dialysis and transplantation techniques in later periods compared to earlier years might have resulted in better survival of patients included in the Dutch and Canadian studies.

Table 23. Results of included studies reporting overall crude all-cause mortality rate/ survival in patients who initiated RRT in childhood

Author (year)	Number of deaths	Overall mortality rate per 100 p/y (95% CI)	Overall survival % (95% CI)
	Age range 0-21 years old		
Wong et al. (2001)[163]	93	3.2 (NR)	NR
Mitsnefes et al. (2013)[120]	**<5 years old** 705 **>5 years old** 2270	**<5 years old** 9.8 (NR) **>5 years old** 3.9 (NR)	NR
Chesnaye et al. (2016)[30]	306	2.8 (NR)	1 year- 96.6 (96.0-97.0) 5 year- 89.5 (87.7-91.0)
Groothoff et al. (2002)[29]	63	1.6 (NR)	5 year-87 (NR) 10 year-82 (NR) 20 year-78 (NR)
McDonald et al. (2004)[118]	436	2.4 (NR)	5 year- 86.0 (84.0-88.0) 10 year-78.0 (76.0-80.0) 20 year-66.0 (63.0-69.0)
Kramer et al. (2009)[166]	76	NR	1 year- 99.4 (99.1-99.7) 5 year- 96.3 (95.3-97.4)
Samuel et al. (2011)[110]	107	1.8 (1.5-2.1)	5 year-91.7 (89.8-93.7) 10 year-85.8 (82.8-88.8)
Chesnaye et al. (2014)[31]	NR	2.0 (NR)	NR
	Age range 0-2 years old		
Alexander et al. (2011)[14]	23	4.7 (2.8-6.6)	1 year-79.8 (71.6-88.8) 5 year-74.9 (66.1-84.8)
Van Stralen et al. (2012)[169]	45	NR	5 year- 76.4 (NR)

p/y-patient years, CI-confidence interval, NR-not reported. Number in superscript refers to the study identifier

Dialysis population, Dialysis and transplanted population

4.3.2.3 CVD incidence and/or CV mortality rate in patients who initiated renal replacement therapy in childhood

Table 24 summarises CV mortality rates and/or CVD incidence reported by the included studies. Only three studies reported CV mortality rates. The Dutch renal registry study (29) reported the overall crude CV mortality rate of 0.95 per 100 p/y (95% CI not reported) in all Dutch children who started RRT between 1972 and 1992 and who survived to adulthood. Another publication using the same cohort with extended follow-up period reported lower CV mortality rates in patients who started RRT from 2000 to 2010 compared to patients who started RRT from 1972 to 1989, 0.22 per 100 p/y (95% CI 0.06-0.56) (165). The authors explained the trend of decreased CV mortality over the last decade by an increased awareness of the burden of CVD in renal patients among clinicians, which may have resulted in better treatment and consequently better survival. Another possible explanation could be a better availability of living-related donors and pre-emptive transplantation in recent decades compared to earlier decades which may in part result in better survival. The USRDS registry (120) reported higher CV mortality rates compared to the Dutch studies of 3.54 and 1.45 per 100 p/y among patients less than 5 years old and older than 5 years old, respectively. The healthier and older study population of RRT patients, who survived into adulthood included in the Dutch studies might explain this difference. Furthermore, the ESRDS registry included dialysis patients only, while the Dutch studies included also transplanted patients who have better survival compared to dialysis population, partly explaining this difference.

Four studies reported data on types of CVD causing the fatal events. The proportion of deaths attributed to CVD ranged from 27.1% to 41.0%. Cerebrovascular accident and cardiac arrest were the most common causes of death from CVD (Table 24).

Despite the high CV mortality in patients who initiated RRT in childhood limited knowledge exists about CVD incidence in this population. Only two studies described incidence of fatal and non-fatal CVD events. The USRDS study (164) only described cardiac events and excluded cerebrovascular disease events. This study included 1,454 incident patients who started dialysis between 0 and 19 years of age. Among them, 452 (31.1%) developed a cardiac-related event (Table 24). Arrhythmia was the most common (19.6%), followed by valvular disease (11.7%), cardiomyopathy (9.6%) and cardiac arrest (3%). A single centre study from Toronto, Canada (109) included 418 patients who received a kidney transplant. The Canadian authors defined CVD incidence as the first fatal or non-fatal CVD event obtained from a hospital admission administrative dataset. CVD events were defined as myocardial infarction, congestive heart failure, cardiac arrest, stroke and transient ischaemic attack. A total of 33 (12.0%) patients had CVD events over mean follow-up of 6.4 years (SD 5.1). Cerebrovascular events accounted for 43% of all CVD events observed. It was impossible to compare this two studies by follow-up period as this data was lacking in the USRDS study (164). It is probable that the study with the longest follow-up period would have highest incidence of CVD.

Table 24. Results of included studies describing overall crude CV mortality rates and CVD incidence in patients who initiated RRT in childhood

Author (year)	Number of CVD events	Crude overall CV mortality rate or CVD incidence per 100 p/y (95% CI)	Proportion of CV deaths or CVD events %	Type of CVD events %
CV mortality				
Groothoff et al. (2002)[29]	26	0.95 (NR)	41.0	Cerebrovascular accident 57.7 Congestive heart failure 15.4 Myocardial infarction 11.5 Cardiac arrest 7.7 Pericarditis 3.8 Aorta dissection 3.8
Mitsnefes et al. (2013)[120]	**<5 years old** 246 **>5 years old** 852	**<5 years old** 3.45 **>5 years old** 1.45	<5 years old 27.1 >5 years old 35.9	**<5 years old** Cardiac arrest 53 Other 47 **>5 years old** Cardiac arrest 49 Other 51
Vogelzanf et al. (2013)[109]	NR	**1972-89** 0.97 (0.58-1.51) **1990-99** 0.37 (0.15-0.76) **2000-2010** 0.22 (0.06-0.56)	NR	NR
CVD incidence				
Chavers et al. (2002)[164]	452	NR	31.1	Arrhythmia 19.6 Valvular heart disease 11.7 Cardiomyopathy 9.6 Cardiac arrest 3.0 Cardiac death 2.8
Koshy et al. (2009)[109]	33	1.07 (NR)	12.0	Cerebrovascular accident 43 Congestive heart failure 33 Myocardial infarction 24

p/y-patient years, CV-cardiovascular, CVD-cardiovascular disease, CI-confidence interval, NR-not reported. Number in superscript refers to the study identifier

4.3.3 Associations of age at start of RRT, sex, PRD, type of RRT and period of initiation of RRT with all-cause mortality and CVD outcomes

This section summarises the results of the associations of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality and CVD outcomes (fatal and/or non-fatal CVD) reported by the included studies.

4.3.3.1 Association of age at start of RRT with all-cause mortality and CVD outcomes in patients who initiated RRT in childhood

Nine studies described the association of age at start of RRT with all-cause mortality and one study described the association of age at death with cardiac mortality (Table 25). Studies were heterogeneous in terms of categorisation of age. The youngest age category varied from <1 years old to <5 years old, while the oldest category varied from >5 years old to 15-19 years old. The results of the studies consistently showed that patients in the youngest age category had a higher risk of all-cause mortality compared to patients in older age category. The USRDS study showed no statistically significant association of age at death with fatal cardiac events among patients who initiated RRT between 0 and 30 years old (149).

Table 25. Results of included studies describing the association of age at start of RRT with all-cause mortality and CVD outcomes in patients who initiated RRT in childhood

Author (year)	Age groups	Effect estimate (95% CI)	Summary of findings
Wong et al. (2001)*[163]	0-2 years 3-14 years 15-18 years	1.00 0.39 (0.21-0.75) 0.39 (0.19-0.80)	Older patients had a lower risk of all-cause mortality compared to the youngest patients.
Groothoff et al. (2002)*[29]	>5 years <5 years	1.00 3.4 (1.8- 6.4)	Patients started RRT less than 5 years of age had a higher risk of all-cause mortality compared to older patients.
Parekh et al. (2002)**[149]	Continuous	Increasing age at death for each 10 years 1.22 (1.00-1.44)	There is no statistically significant association between age at death and cardiac mortality.
Kramer et al. (2009)*[166]	15-17 years 10-14 years 5-9 years 0-4 years	1.00 0.99 (0.58-1.69) 1.39 (0.70-2.77) 1.19 (0.28-5.05)	There is no statistically significant association between age at start of RRT and all-cause mortality.
Alexander et al. (2011)*[14]	1-2 years 3 months-1 year <3 months	1.00 2.48 (0.67-9.20) 4.37 (1.21-15.80)	Patients started RRT at the age of less than 3 months had a higher risk of all-cause mortality compared to those who started RRT from 1 to 2 years old.
Samuel et al. (2011)*[110]	10- <18 years 1 to <10 years <1 year	1.00 1.47 (0.70-3.12) 7.82 (3.97-15.44)	Patients who started dialysis at the age of less than 1 year had a higher risk of all-cause mortality compared to those started RRT from 10 to 18 years old.
Mitsnefes et al. (2013)*[120]	Continuous variable	<5 years HR/year 0.75 (0.70-0.80) >5 years HR/year 1.00 (0.99-1.02)	Each one-year increase in age in patients started RRT less than 5 years old was associated with a lower risk of all-cause mortality.
Pruthi et al. (2013)*[168]	12-16 years 8-11 years 4-7 years 2-3 years 0-1 years	1.00 1.19 (0.52-2.71) 1.48 (0.65-3.34) 2.69 (1.20-6.02) 5.13 (2.62-10.03)	Patients started RRT from 0 to 3 years old had a higher risk of all-cause mortality compared to the oldest patients.
Chesnaye et al. (2015)*[164]	15-19 years 10-14 years 5-9 years 0-4 years	1.00 1.1 (0.6-1.9) 1.4 (0.8-2.4) 4.4 (2.8-7.0)	The youngest age group had the highest risk of all-cause mortality compared to the oldest patients.

Author (year)	Age groups	Effect estimate (95% CI)	Summary of findings
Carey et al. (2016)*[167]	<1 month 1-24 month	1.00 0.80 (0.56-1.14)	There is no statistically significant association between age at start of RRT and all-cause mortality.

CI-confidence interval, RRT-renal replacement therapy, * effect estimates presented as adjusted hazard ratios,** effect estimates presented as adjusted odds ratios, number in superscript refers to the study identifier

Association of age at start of RRT with all-cause mortality,

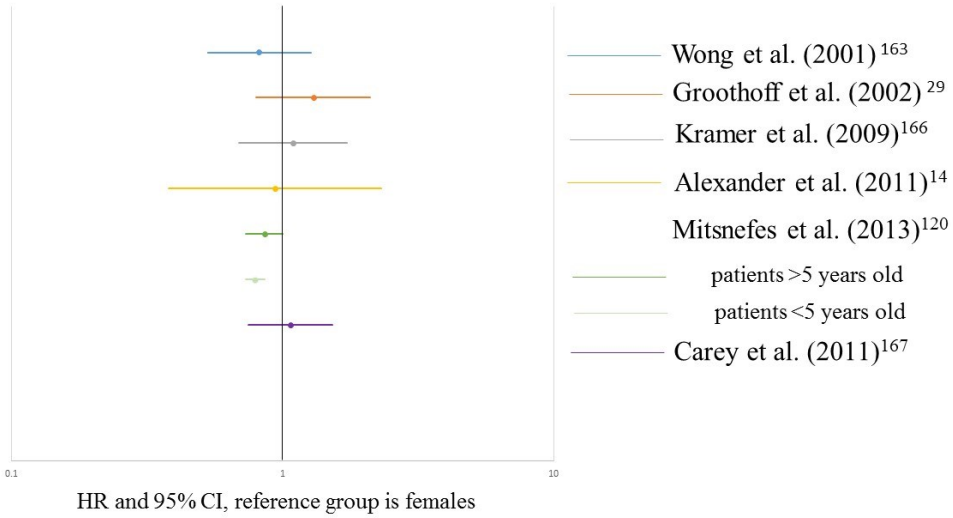
Association of age at death with cardiac mortality (myocardial infarction, cardiac arrest, cardiomyopathy, arrhythmias, pericarditis, valvular heart disease and other cardiac causes)

4.3.3.2 Association of sex with all-cause mortality and CVD outcomes in patients who initiated RRT in childhood

Six studies described the association of sex with all-cause mortality (Figure 31) and one with cardiac mortality (149). Almost all studies showed no statistically significant association of sex with all-cause mortality apart from the USRDS that reported that male patients had a 20% significantly lower risk of all-cause mortality compared to female patients among those who started RRT older than five years old. However, the authors did not find a significant association among patients younger than five years old (120).

The only USRDS study that described the association of sex with cardiac mortality (not in the Figure, described in the text only) showed no statistically significant association among patients who initiated RRT between 0 and 30 years old, OR 1.17 (95% CI 0.9-1.5) (149).

Figure 31. Association of sex with all-cause mortality reported in the studies



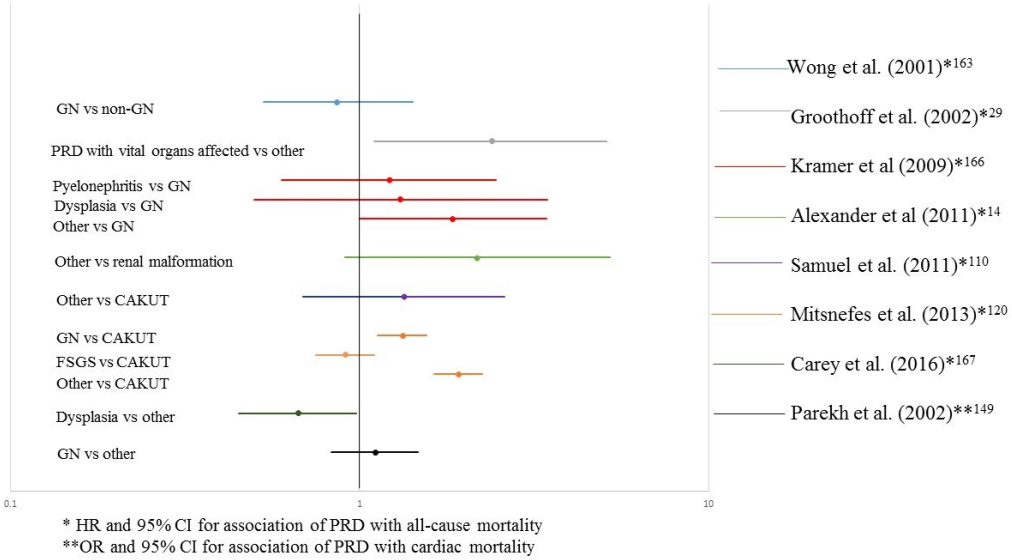
4.3.3.3 Association of PRD with all-cause mortality and CVD outcomes in patients who initiated RRT in childhood

Seven studies described the association of PRD with all-cause mortality and one with cardiac mortality (149) in patients who initiated RRT in childhood (Figure 32). Three studies reported a statistically significant association showing that patients with CAKUT have a lower risk of all-cause mortality compared to other PRD. For example, the Dutch study showed that patients with Goodpasture's syndrome, oxalosis, cystinosis or autosomal recessive polycystic kidney disease had a higher risk of all-cause mortality compared to patients with CAKUT, HR 2.4 (95% CI 1.1-5.1) (29). The USRDS study showed that patients with GN and patients with PRD other than GN or focal segmental glomerulosclerosis had a higher risk of all-cause mortality compared to patients with CAKUT, HR 1.49 (95% CI 1.08-2.04) and HR 1.35 (95% CI 1.11-1.63), respectively (120). Similarly, the NAPRTCS study also reported that patients

with CAKUT had a lower risk of all-cause mortality compared to patients with other PRD, HR 0.67 (95% CI 0.45-0.98) (167).

The only study that described the association of PRD with CVD outcome was the USRDS study (149). The authors categorised PRD as glomerular or other types of PRD, which included diabetes, hypertension, polycystic kidney disease, obstructive uropathy/dysplasia and other. The authors did not find a statistically significant association between PRD and cardiac mortality.

Figure 32. Association of PRD with all-cause mortality and CVD outcomes reported in the included studies



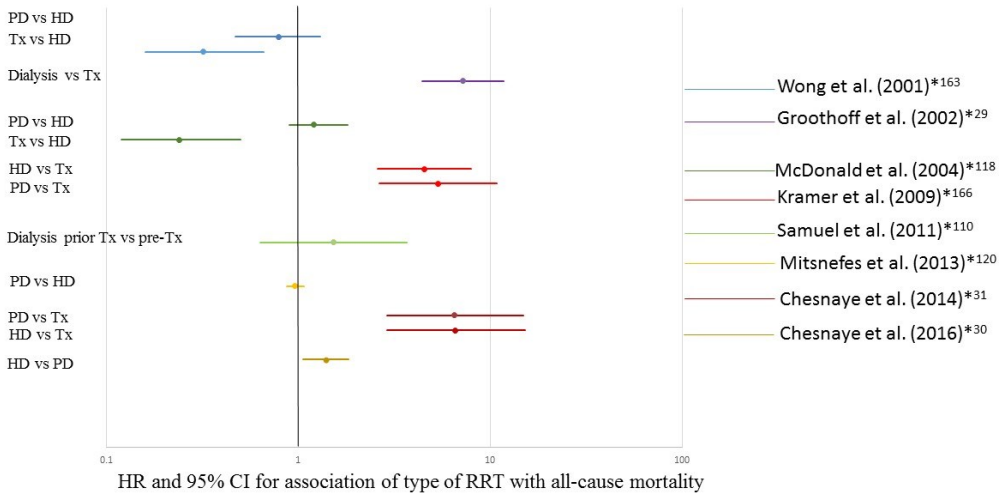
* HR and 95% CI for association of PRD with all-cause mortality
**OR and 95% CI for association of PRD with cardiac mortality

4.3.3.4 Association of type of RRT with all-cause mortality and CVD outcomes in patients who initiated RRT in childhood

Eight studies described the association of type of RRT with all-cause mortality (Figure 33) and three described the association of type of RRT with CVD outcomes (Figure 34). Studies that included both dialysis and transplanted populations consistently showed that patients receiving pre-emptive transplantation or a kidney transplant during follow-up period had a lower risk of all-cause mortality compared to patients only receiving dialysis. There were two studies including dialysis populations that investigated the association of PD and HD with all-cause mortality, the ESPN/ERA-EDTA (30) and the USRDS (120). Only the ESPN/ERA-EDTA study showed statistically significant results, reporting that patients who initiated RRT with HD had a higher risk of all-cause mortality compared to patients initiated RRT with PD. One of the limitations of the ESPN/ERA-EDTA study was a short median follow-up period

of 2.17 years (IQR not reported). The USRDS registry did not report the follow-up period.

Figure 33. Association of type of RRT with all-cause mortality

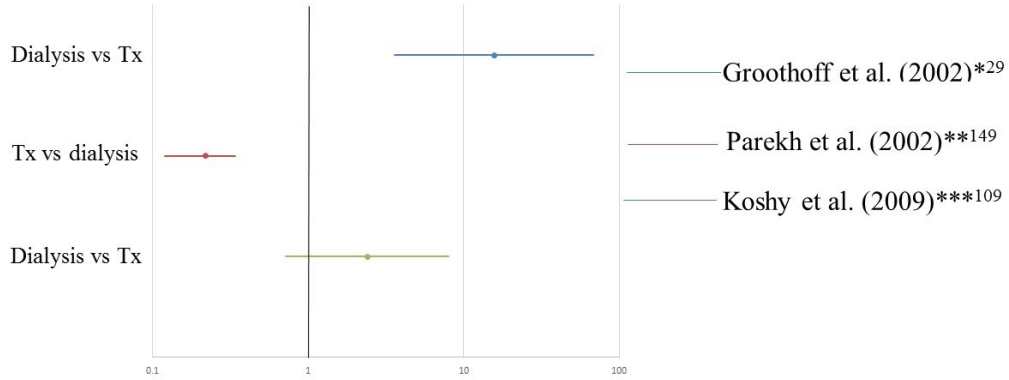


Three studies described association of type of RRT with CVD outcomes (Figure 34). All three studies used different CVD outcomes. Two studies used only fatal CVD events (29, 149). The Dutch study used cerebrovascular mortality (29), while the USRDS study (149) used cardiac mortality, defined as myocardial infarction, cardiac arrest, cardiomyopathy, arrhythmias, pericarditis, valvular heart disease and other cardiac causes. The Canadian study used fatal and non-fatal CVD events as their outcome (109).

The Dutch and the USRDS studies both showed that transplanted patients had a lower risk of cerebrovascular and cardiac mortality, respectively, compared with dialysis patients. However, the Canadian study did not find a statistically significant difference in CVD incidence between transplanted patients who started on dialysis and pre-

emptively transplanted patients possibly due to the small sample size (N=274) and small number of CVD events (N=33) resulted in low statistical power.

Figure 34. Association of type of RRT with CVD outcomes



* HR and 95% CI for association of type of RRT with cerebrovascular mortality
**OR and 95% CI for association of type of RRT with cardiac mortality
***HR and 95% CI for association of type of RRT with CVD incidence

4.3.3.5 Association of period of initiation of RRT with all-cause mortality and CVD outcomes in patients who initiated RRT in childhood

Five studies described the association of period of initiation of RRT with all-cause mortality and three with CV mortality. (Table 26). However, only three studies found statistically significant results (118, 120, 165). These results showed that patients who initiated RRT in recent periods had a lower risk of all-cause and CV mortality compared to patients who initiated RRT in earlier periods. The ANZDATA registry (118) reported that patients commencing RRT from 1963 to 1982 had a significantly higher risk of all-cause mortality compared to those who started RRT from 1993-2002. The USRDS (120) included patients who started RRT from 1990 to 2010 reporting that each 5 year increment in calendar year of dialysis initiation is associated with a

lower risk of all-cause and CVD mortality. The Dutch study (165) showed that patients who started RRT from 1990 to 2010 had a lower risk of CVD mortality compared to those started RRT from 1972 to 1989.

Table 26. Results of included studies describing the association of period of initiation of RRT with all-cause/CV mortality in patients who initiated RRT in childhood

Author (year)	Period of initiation of RRT	Crude HR (95% CI)	Summary of findings
Groothoff et al. (2002)[29]	1972-1981 1982-1991	1.3 (0.8-2.1) 1.00	There is no difference in all-cause and CV mortality between patients who started RRT in the period from 1982 to 1991 compared to those who started RRT from 1972 to 1981
	1982-1991 1972-1981	0.4 (0.2-1.0) 1.00	
McDonald et al. (2004)[118]	1963-1972 1973-1982 1983-1992 1993-2002	4.2 (2.3-6.0) 2.0 (1.3-3.5) 1.4 (0.9-2.1) 1.00	Patients commencing RRT from 1963 to 1982 had a significantly higher risk of all-cause mortality compared to those who started RRT from 1993-2002
Samuel et al. (2011)[110]	2000-2007 1992-1999	1.18 (0.69-2.03) 1.00	There is no difference in all-cause mortality between patients started RRT in the period from 2000 to 2007 compared to those who started dialysis from 1992-1999
Mitsnefes et al. (2013)[120]	Continuous 1990-2010	HR per 5 years increment in calendar year of RRT initiation **Patients <5 years old** 0.82 (0.77-0.87) **Patients >5 years old** 0.88 (0.85-0.92)	Each 5 years increment in calendar year of dialysis initiation is associated with a lower risk of all-cause and CV mortality
		Patients <5 years old 0.54 (0.47-0.63) **Patients >5 years old** 0.66 (0.61-0.70)	
Vogelzang et al. (2013)[165]	2000-2010 1990-1999 1972-1989	0.09 (0.02-0.45) 0.26 (0.10-0.66) 1.00	Patients who started RRT from 1990 to 2010 had a lower risk of CV mortality compared to those who started RRT from 1972 to 1989
Carey et al. (2016)[167]	1992-1998 1999-2005	1.30 (0.88-1.91) 1.00	There is no difference in all-cause mortality between patients who started dialysis from 1992 to 1998 compared to patients who started from 1999 to 2005

HR hazard ratio, RRT-renal replacement therapy, CV-cardiovascular, ESRD-end stage renal disease, CI-confidence interval, number in superscript refers to the study identifier

Association of period of start of RRT with all-cause mortality

Association of period of start of RRT with CV mortality

4.3.4 Quality assessment of the included studies

4.3.4.1 Internal validity of the studies

Volunteer bias

Studies by van Stralen et al. (169) and Carey et al. (167) may have been affected by volunteer bias as both studies used voluntary registries, the IPPN and the NAPRTCS, respectively. Both registries have been described in more detail in previous chapters. Since there is no information available about non-participating centres it is difficult to predict the direction of the selection bias.

Selection bias

Most of the studies included all eligible patients, apart from a few studies that excluded patients from the analyses due to missing data or loss to follow-up. For example, the two studies performed by the USRDS registry excluded 12.3% (163) and 6% (149) of patients with missing data from the analyses. The ANZDATA registry study (118) excluded 2% of patients who were lost to follow-up in their analyses. The Canadian study (109) that reported the association of type of RRT with CVD incidence excluded 5% of patients with missing ID that was necessary for data linkage.

The characteristics of patients with missing data that were excluded from the analyses were not provided in all studies. Therefore, it is impossible to predict the direction of any selection bias and its effect on the internal validity of the studies. However, it is unlikely that such small proportion of excluded patients from the analyses would impact on the findings in the above studies.

Misclassification bias

It is unlikely that misclassification of all-cause mortality would occur in the studies; however, cause specific mortality might be misclassified. Most studies used registry data submitted by participating centres through death certificates, which tend to overestimate CV cause of death compared to deaths that were validated by autopsy (156).

Survival bias

The potential source for survival bias was identified in the majority of studies. Two Dutch studies by Groothoff et al.(29) and Vogelzang et al.(165) used the same cohort of patients who started RRT in childhood and survived into adulthood defined as older than 18 years old by the time of the study initiation. Another study from the ERA-EDTA (166) that also selected patients who started RRT in childhood and reached the age of 18 years. Inclusion of healthier population of RRT patients results in better survival and likely explains the lower mortality rates reported by these studies.

The studies that included the youngest patients (14, 167, 169) and/or patients receiving dialysis (30, 120, 163, 164, 167) are also subject to survival bias because over time older and healthier children receive a kidney transplantation. Inclusion of sicker RRT populations might partly explain the higher mortality rates in these studies. Survival bias may also affect the studies with short follow period (14, 31, 168) as most deaths usually occur among the youngest patients and within the first year after start of RRT.

Confounding

Most studies adjusted their associations for important confounding factors. However, some studies might over-adjust their results. For example, in the association of sex

with all-cause mortality age at start of RRT is not a confounding factor as it is associated with the outcome but not with the exposure. Therefore, it represents another risk factor and should not be adjusted for. In the association of PRD with all-cause mortality type of RRT might be in a causal pathway, as patients with more severe PRD might start with dialysis and healthier patients might receive a kidney transplant.

4.3.4.2 External validity of the studies

The ESPN/ERA-EDTA (30, 31), the ERA-EDTA (166), the National Dutch Registry of patients on RRT (29, 165), the Canadian Paediatric ESRD registry (14, 110), the ANZDATA (118) and the UK renal registry (168) studies have a high generalisability of their findings due to national coverage of these registries and very low proportion of excluded patients from their analyses. However, the results of the USRDS studies (120, 163, 164) can only be extrapolated to the Medicare eligible population as the analyses was restricted to Medicare patients registered in the USRDS registry.

The only single centre study from the Sick Kids hospital in Province of Ontario, Canada reported that their hospital performs all paediatric kidney transplants in Ontario which covers 40% of the population of Canada (109). It is not possible to say whether patients who were transplanted in this hospital are representative to all paediatric patients receiving a kidney transplantation in Canada as the authors do not provide this information about this hospital.

4.4 Discussion

4.4.1 Summary of findings of the literature review and limitations of the studies

All-cause mortality/survival and fatal/non-fatal CVD outcomes

This literature review including 16 observational studies mostly from known renal registries (14, 29-31, 110, 118, 120, 149, 163-169) showed that all-cause mortality rates varied widely across studies (1.6-9.8 per 100 p/y) partly due to the heterogeneous study populations. The studies either included dialysis or transplanted patients or patients from specific age group. Studies that included dialysis or younger RRT populations reported higher mortality rates compared to the studies that included transplanted or older RRT populations. Most studies reported five-year survival or shorter, while only few studies described very long-term survival. The results of these studies may suffered from survival bias due to inclusion of selected RRT populations that also limits generalisability of their results to a wider paediatric RRT populations.

Only a few studies reported CV mortality rates. Despite the fact that CVD was one of the most common causes of death only very limited information was identified through this literature review. The most commonly reported fatal and non-fatal CVD events in the studies were cerebrovascular disease and cardiac arrest/arrhythmias.

Association of age at initiation of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality and CVD outcomes

Data about the associations between determinants and all-cause mortality is sparse. A few studies showed that patients with CAKUT, receiving a kidney transplant, older

age at start of RRT and initiating RRT in recent periods are associated with a lower risk of all-cause mortality. Only a few studies described the associations between determinants and CVD outcomes. The studies mostly used fatal CVD events as the outcome, with the definition varying between studies as CVD mortality, cerebrovascular mortality and cardiac mortality. Only two studies, the Canadian (109) and the USRDS (164), used non-fatal and fatal CVD events, while only the Canadian study (109) described the association of RRT with CVD incidence and included only transplanted RRT populations. Therefore, I have identified that there is a very limited information published about the associations of age at initiation of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality and CVD incidence in patients who initiated RRT in childhood.

Since completion of this literature review one recent additional paper has been identified performed by the UK renal registry (170). This study included patients who started RRT from 11 to 30 years old between 1999 and 2008. The authors reported that five year survival was worse among older patients (26-30 years old) compared to younger patients. This is explained by the older RRT population included in this study compared to the studies described in this literature review. The authors reported a changing pattern from CAKUT in childhood to increasing diabetes, hypertension and renovascular diseases in adulthood. The proportion of ESRD due to diabetes in patients from 26 to 30 years old was 17.4%. This study also showed that patients with diabetes have an increases risk of all-cause mortally compared to patients with glomerular diseases (170).

4.4.2 Limitations of the literature review

Due to time restrictions, only papers published from 2011 to 2016 were searched. Therefore, papers published earlier than 2011 were not identified by the search. However, I successfully identified articles based on data from the known national and international registries, which are likely to be the key sources of the highest quality data in studies reporting on this topic. Furthermore, inclusion of recent papers to the review reflects current clinical practice compared to older papers. The results from older papers could be difficult to extrapolate to the current clinical practice due to change in RRT population over time and improvement in dialysis techniques and transplantation. Therefore, I expect that I identified the major large and most valid studies. Similarly to the systematic review in Chapter 2, other databases, such as the nursing data base CINAHL, the Latin American database LILACS and the Chinese databases were not searched, and only English language papers were sought. Therefore, not all relevant studies might have been identified. However, most relevant studies in this area are likely to be published in English and in journals that are included in Medline or Embase because the major registries studies are within English speaking countries or European countries where scientific research is usually published in English language journals.

Since this literature review was performed to inform the SRR analyses (Chapter 5 and 6) the particular determinants (age at start of RRT, sex, PRD, type of RRT and period of start of RRT) were of interest partly because these were the risk factors that are available and would be investigated within the SRR analyses. Another important risk factor for mortality that was not included in this review is race/ethnicity. Previous research from the ESPN/ERA-EDTA registry showed that Asian patients had higher

overall mortality risk on RRT compared with white patients (HR, 2.50; 95% CI, 1.14-5.49) (171).

4.5 Conclusion and future research

There is little data available on the long- to very long-term survival and CVD incidence among patients who initiated RRT in childhood. The available studies might suffer from selection/survival bias as they generally are based on selected RRT populations and followed patients up for five years or less. The information about CVD incidence and the associations of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality and CVD incidence is limited. Therefore, future studies are needed reporting on very long-term survival, CVD incidence and the association between the determinants and all-cause mortality and CVD incidence to provide relevant information on prognosis for sub-groups of paediatric RRT populations.

To be able to address identified gaps in the literature the SRR was chosen as a source of routine data for adult and paediatric patients who receive RRT for ESRD in Scotland. The SRR provides the opportunity to follow-up patients over a long period of time, including into adulthood. Moreover, the SRR contains patient data such as sex, date of birth, initial RRT modality, start of RRT date, switches of RRT, PRD, date of death and cause of death. The SRR can be linked to other national registries such as hospital admissions and mortality records to study CVD incidence in this population. Therefore, the SRR data were used to describe the long-term survival, all-cause mortality and CVD incidence in patients who initiated RRT in childhood. The results of these analyses are presented in the next chapters. Chapter 5 is a methodology

chapter that describes SRR and the linkage of the SRR data with hospital admissions and mortality records. Chapter 6 presents analyses of SRR data on survival/mortality and the associations of age at start of RRT, sex, PRD, type of RRT and period of start of RRT and with all-cause mortality in patients who initiated RRT in childhood in Scotland. Chapter 7 presents data on CVD incidence and the associations between the same set of determinants and CVD incidence in patients who initiated RRT in childhood in Scotland.

Chapter 5. Scottish Renal Registry: data linkage, cohort selection and analytical approach

5.1 Background and aim of the study

The literature review presented in Chapter 4 showed that limited knowledge exists about long-term survival in patients who initiate RRT in childhood. The available studies generally included selected RRT populations either limited to people receiving dialysis or to kidney transplant recipients or to specific age groups. This means that these studies could not assess the difference in mortality between patients receiving different RRT type or between younger and older patients. I found a few studies that included both dialysis and transplanted patients as well as patients of all age groups from 0 to 18 years old. However, these studies were limited to short follow-up. Furthermore, few data are available about the association of age at initiation of RRT, sex, type of RRT, PRD and period of start of RRT with all-cause mortality among children who receive RRT. Selection bias in some studies might have led to underestimation or overestimation of the associations that were described. Moreover, information on causes of death might be biased due to misclassification as almost all studies had missing data on causes of death. Therefore, the overall aim of this study is to describe the long-term survival, all-cause mortality, causes of death and CVD incidence in a nationally representative cohort of patients who initiated RRT in childhood.

The specific objectives are:

1. To describe the demographic characteristics, long-term survival, all-cause mortality, cause of death and CVD incidence in patients who initiated RRT in childhood in Scotland;

2. To describe the association of age at initiation of RRT, sex, type of RRT, PRD and the period of commencing RRT with all-cause mortality/CVD incidence in patients who initiated RRT in childhood in Scotland.

I used an extract of the SRR (described below) linked to the national registry of causes of death and hospital admissions to address this aim and the objectives.

5.2 Choice of Scottish Renal Registry and comparison with other renal registries

The SRR is a national registry of both adult and paediatric patients receiving RRT for ESRD in Scotland. Data from Scottish renal units are available from 1961, which is the year routine RRT for ESRD started in Scotland. Up to 31st December 2015, 16,741 patients have started RRT in Scotland. Compared to the ESPN/ERA-EDTA, the SRR dataset includes a much smaller sample size as it only collects data from Scotland. However, one of the advantages of the SRR is the long-term follow-up as the SRR includes data for children who receive RRT and continues to collect data for survivors to adulthood who remain under follow-up in Scotland.

In comparison to other known national and international renal registries (17, 19, 22) the SRR was considered the best options for this thesis for several reasons. The first reason to use the SRR is that all National Health Service (NHS) renal units contribute fully to the SRR leading to national coverage of patients receiving RRT for ESRD in Scotland and its results are generalisable to all patients who initiate RRT for ESRD in

Scotland. In contrast, the USRDS registry limits their analyses to Medicare patients only (17) and the coverage of the IPPN registry differs widely between participating countries (22). This means their results are not generalisable to the entire RRT population. Also, the incidence of RRT is higher among the US population compared to the European population (17, 172), therefore, it would be inappropriate to directly extrapolate the USRDS registry results to the European population.

Furthermore, the major advantage of using SRR data is the feasibility of data linkage. Data linkage systems exist in only a handful of countries or regions including Australia, Canada, Norway, Sweden, Finland, England, Scotland and most recently in Wales (173). It was possible to obtain data on incident CVD events of patients registered in the SRR through linking their records with causes of death and CVD hospital admissions data.

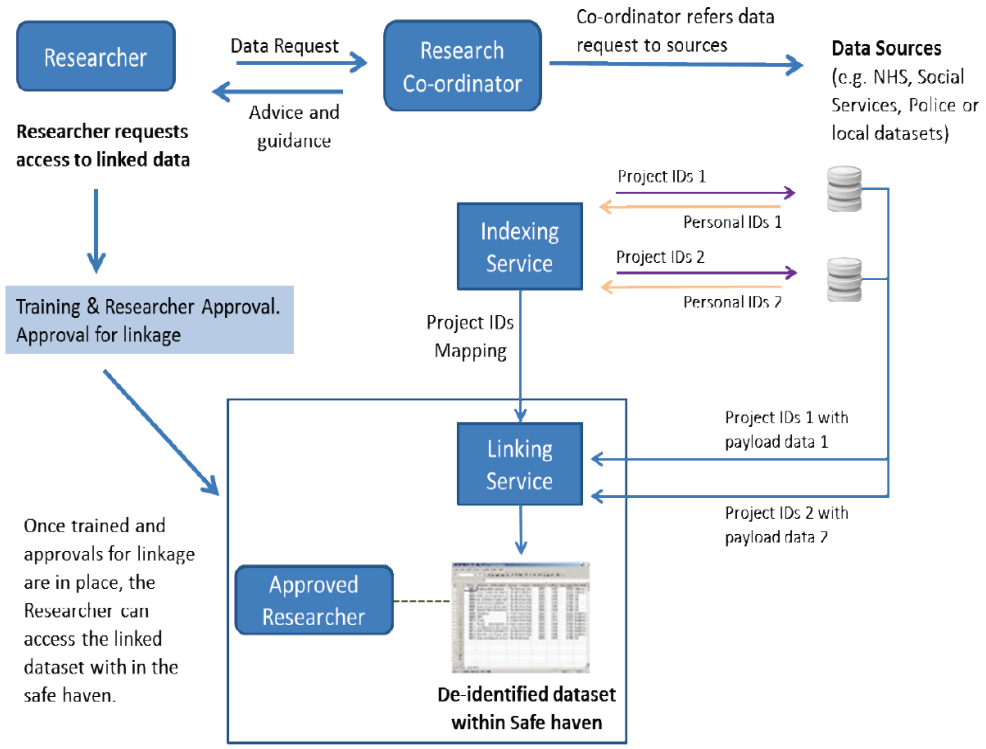
5.3 Data request and data linkage

A request form for the release of data from the SRR was submitted to the SRR steering group (Appendix 2, page 382). Additionally, a Self-Audit Checklist for Level 1 Ethical Review for PGR projects, Centre for Population Health Sciences research ethics subgroup was submitted (Appendix 2, page 390). I completed data governance training as a requirement for accessing the data (see Appendix 2 page 396 for certificates). I applied to the Public Benefit and Privacy Panel for Health and Social Care (PBPP) for permission to use SRR data linked to causes of death and hospital admissions records (Appendix 2 page 398). All applications were approved. PBPP is a governance structure of NHS Scotland, which undertakes information governance scrutiny of

requests to access NHS Scotland-originated data for a variety of purposes, one of which is data linkage with other sources.

SRR datasets were sent to the Electronic Data Research and Innovation Service (eDRIS) indexing team with The Community Health Index (CHI) numbers for all patients in the file. CHI number is used to link records from different datasets. The CHI number is the unique patient identifier used in all primary health care activities and hospital based clinical information systems, throughout NHS Scotland (174). To ensure that privacy is maintained researchers can only see the final results from the data linkage via Scotland's safe havens (Figure 35).

Figure 35 An overview of the data linkage process



Source of image: "A Health and Biomedical Informatics Research Strategy for Scotland. Enhancing research capability in health informatics for patient and public benefit 2015-2020, page 15".

For the purpose of this thesis the SRR data has been linked with the Scottish Morbidity Records (SMR01) and causes of death (174). The CHI numbers were replaced with the Master Index number on the SRR, death and hospital admission datasets. I could then use this number to link the data files from SRR, mortality records and hospital admission data. Records of causes of death and CV hospital admissions were available from 1 January 1981 to 31 December 2015 because electronic information on death records and hospital admissions is available from 1981 onwards.

All patient data were anonymised before being released to me for the analyses. Date of birth was given as month and year, to protect confidentiality. The costs for data access to the Safe Haven were covered by my and my supervisor`s (Sarah Wild) research funds (total £3,509).

5.4 Cohort design and study time frames

Study time frames

As the SRR analyses is focused on patients who initiated RRT in childhood I requested data on all 479 patients registered in the SRR who initiated RRT from 0-<18 years of age between January1961 and 31st December 2013. The end date of 31st December 2013 reflected the most recent available mortality linked data at the time of the data request. Causes of death and CVD hospital admissions are available from 1981, hence the analyses of cause of death and CVD incidence were limited to the 403 patients who initiated RRT from 1981 to 2013 (Figure 36).

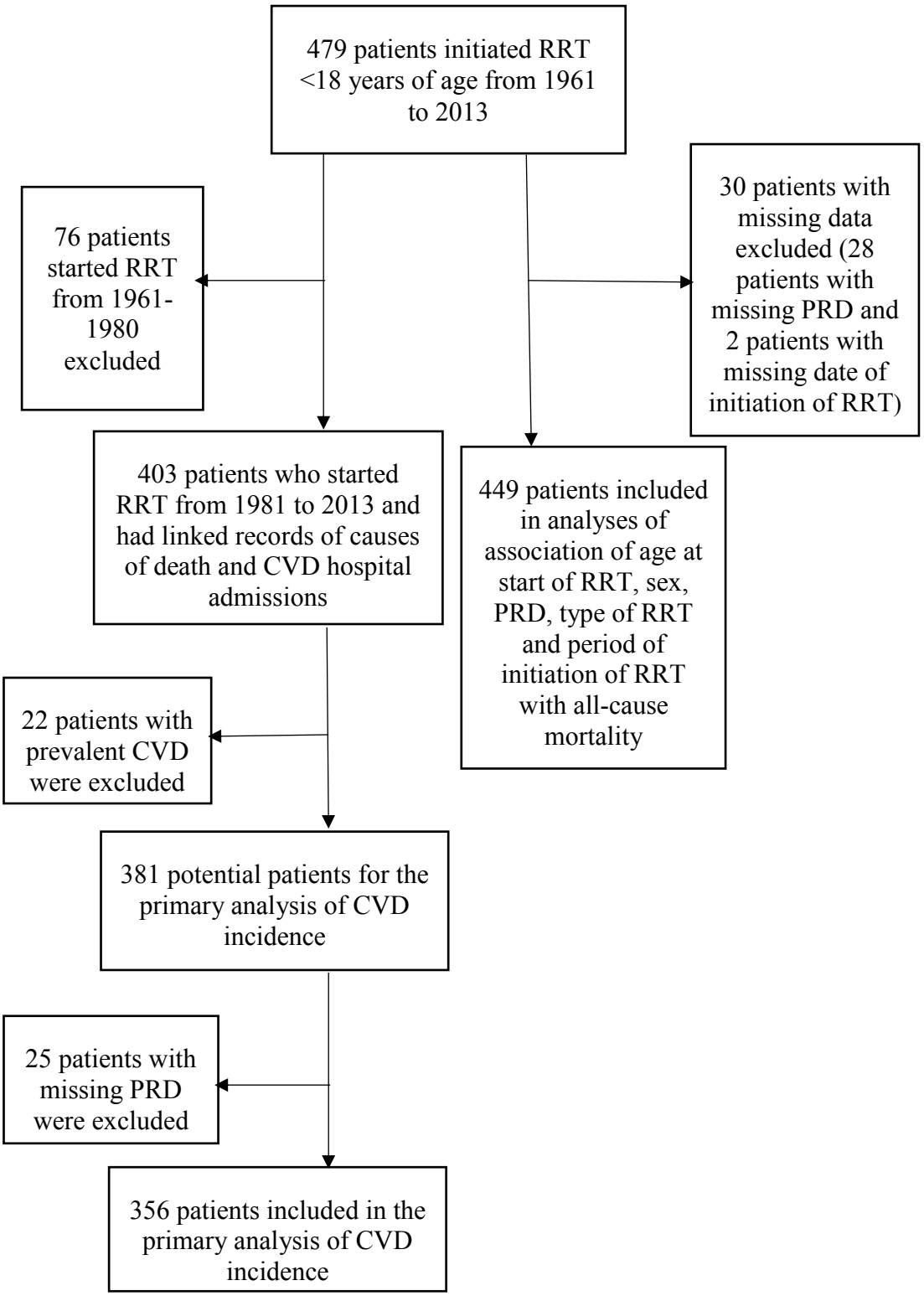
Cohort design

As the aim of this study is to describe mortality/CVD incidence and associated risk factors over a follow-up period a cohort study is the best suitable study design as opposed to cross-sectional or case-control studies which measure the association between exposure and outcome at a certain time point. Furthermore, cross-sectional studies are subject to survival bias as patients who may have died before the beginning of the study would not be included to the study. This is a retrospective cohort study because conducting a prospective cohort study would not be possible as I would need to start including participants into the study from the beginning of my PhD onwards. Due to the rarity of RRT in children and small number of events (death and CVD events) it was not feasible. The cohort is open as patients could enter and exit the study at any time point within the observation period.

Longitudinal data

One of the challenges related to the longitudinal nature of the study is handling repeated measurements. For example, in the ESPN/ERA-EDTA analysis presented in Chapter 3 I summarised repeated CVRFs measurements into one summary value. In contrast, this study is not focused on CVRFs, however, patients could change RRT modalities over follow-up period. The approach chosen to handle RRT changes over follow-up period is described below in section 5.8.4.

Figure 36 Flow chart describing numbers of included and excluded patients for the final analysis of all-cause mortality, cause of death and CVD incidence among children receiving RRT and registered in the SRR



5.5 Period of follow-up

Patients were followed from the start of RRT until death for the analysis of all-cause mortality or first CVD event for the analysis of CVD incidence, or the end of observation period (December 31st, 2015) or lost to follow-up, whichever came first (Figure 37, 38).

Figure 37 A diagram of depicting how patients are included in follow-up or lost to follow-up for all-cause mortality analysis

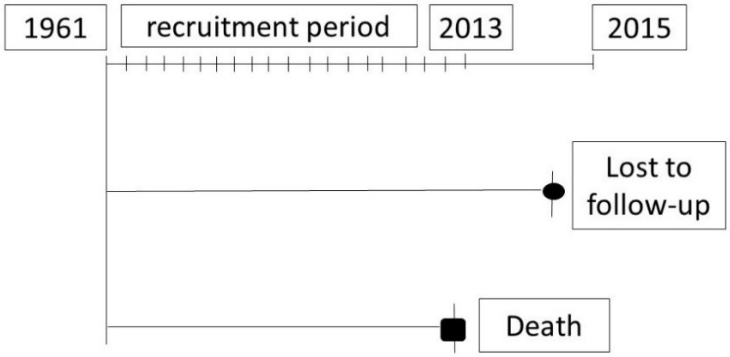
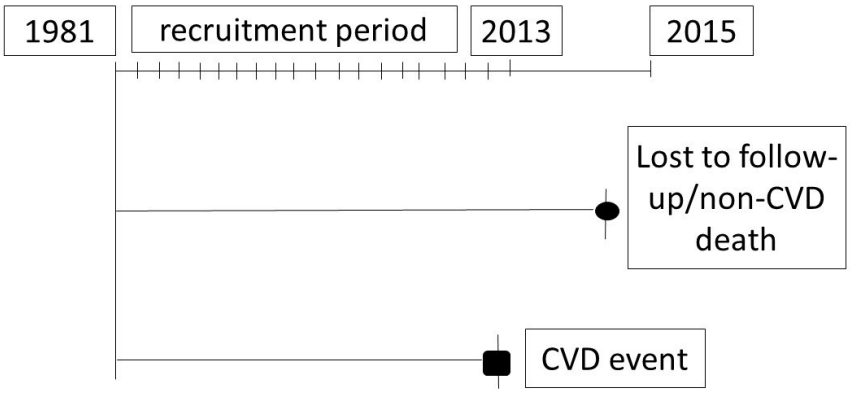


Figure 38 A diagram of depicting how patients are included in follow-up or lost to follow-up for CVD incidence analysis



5.6 Data collection within SRR and missing data

Each renal unit elects one consultant nephrologist to submit data electronically to SRR. Within the SRR, data on individual RRT patients are collected annually, including information on date of birth, sex, PRD, type of RRT, date of first RRT, changes of RRT, and date and cause of death. Almost all variables were complete apart from PRD which was missing in 6.2% of patients. Imputation of missing data could not be performed as one of the main assumption for imputation is that data are missing at random. It might be that patients with missing PRD were more complicated patients with the PRD diagnoses that could not be confirmed without further instrumental/laboratory tests. Therefore, at the moment of data submission this information could be missing. Thus, it is likely that data were missing not at random. For this reason, a complete case analysis was performed. The patients with missing data were excluded from all survival analyses (Cox regression and Kaplan-Meier) (Figure 36). To check whether these exclusions might introduce bias, the characteristics of patients with missing data were compared to the sub-cohort with complete data.

5.7 Definition of outcomes

5.7.1 All-cause mortality

The SRR has data on vital status for all 479 patients. Therefore, this information was used to describe all-cause mortality rate.

5.7.2 Cause of death

Cause of death was assigned using information given in the primary position of death certificates. Cause of death was classified according to the ERA-EDTA coding system (172), to again facilitate comparisons with previous studies: circulatory disease, infection, malignancies, renal and other. International classification of diseases ICD-9 (175) and ICD-10 (176) codes for each category are presented in Table 27.

Table 27. ICD-9 and ICD-10 codes used for definition of causes of death

Cause of death	ICD-9 Codes	ICD-10 Codes
Circulatory disease	390-459	I00-I99
Infection	001-139, 460-466, 480-488, 560-569	A00-B99, J00-J22, K65-K67
Malignancies	140-239	C00-D48
Renal	580-599, 753	N00-N39, Q60-Q64
Other	240-389, 470-478, 490-558, 570-579, 600-752, 754-999	D50-H95, J30-J99, K00-K64, K70- M99, N40-N99, O00-Q56, Q65-Z99

Deaths due to circulatory diseases listed in any position of death certificates were also identified and were grouped as follows: Ischaemic heart disease, cerebrovascular disease, heart failure, cardiac arrest/arrhythmias, cardiomyopathy and other diseases of circulatory system. ICD-9 and ICD-10 codes for each category is presented in Table 28. These groups were chosen to make the results of this study comparable with other literature as most of the previous research picked these CVD events, which are also the most clinically important events.

Table 28. ICD-9 and ICD-10 codes used for classification of causes of death due to circulatory disease

Type of CV death	ICD-9 Codes	ICD-10 Codes
Ischaemic heart disease	410-414	I20-I25
Cerebrovascular disease	430-438	I60-I69
Heart failure	428	I50
Cardiac arrest/arrhythmias	427	I46-I49
Cardiomyopathy	425	I42, I43
Other diseases of circulatory system	390-405, 415-417, 420-424, 426, 429, 440-459	I00-I15, I26-I28, I30-I41, I44, I45, I51, I52, I70-I99

5.7.2 CVD incidence

CVD incidence was defined as the first CVD event, either fatal or non-fatal, whichever came first. Fatal CVD events were defined as any circulatory disease as identified from ICD-9 (390-459) codes on death records before 1997 and ICD-10 (I00-I99) codes for subsequent years. Non-fatal CVD events were defined similarly but with exclusion of codes for hypertensive disease (401, 403, and 405 for ICD-9 and I10, I12, I15 for ICD-10) and arteriovenous fistula (447 for ICD-9 and I77.0 for ICD-10). CVD codes were identified from any position listed in the diagnoses in hospital admissions records or death certificates. Table 38 presents ICD-9 and ICD-10 codes for selected key CVD sub-types of ischaemic heart disease, cerebrovascular disease, heart failure, cardiac arrest/arrhythmias, cardiomyopathy and other diseases of the circulatory system.

Table 29. ICD-9 and ICD-10 codes used for fatal and non-fatal CVD events

CVD events	Non-fatal CVD events		Fatal CVD events	
	ICD-9	ICD-10	ICD-9	ICD-10
Ischaemic heart disease	410-414	I20-I25	410-414	I20-I25
Cerebrovascular disease	430-438	I60-I69	430-438	I60-I69
Heart failure	428	I50	428	I50
Cardiac arrest/ arrhythmias	427	I46-I49	427	I46-I49
Cardiomyopathy	425	I42, I43	425	I42, I43
Other diseases of circulatory system	390-398, 402, 404, 415-417, 420-424, 426, 429, 440-446, 448-459	I00-I09, I11, I13, I26-I28, I30-I41, I44, I45, I51, I52, I70-I74, I77.1-I99	390-405, 415-417, 420-424, 426, 429, 440-459	I00-I15, I26-I28, I30-I41, I44, I45, I51, I52, I70-I99

5.7.2.1 Secondary analysis of CVD incidence

A secondary analysis was performed in two steps: first, applying a stricter definition of CVD incidence by excluding the group of other non-fatal diseases of the circulatory system from the definition (Table 39).

Table 30. ICD-9 and ICD-10 codes used for fatal and non-fatal CVD events in the secondary analysis

CVD events	Non-fatal CVD events		Fatal CVD events	
	ICD-9	ICD-10	ICD-9	ICD-10
Ischaemic heart disease	410-414	I20-I25	410-414	I20-I25
Cerebrovascular disease	430-438	I60-I69	430-438	I60-I69

Heart failure	428	I50	428	I50
Cardiac arrest/arrhythmias	427	I46-I49	427	I46-I49
Cardiomyopathy	425	I42, I43	425	I42, I43
Other diseases of circulatory system	-	-	390-405, 415-417, 420-424, 426, 429, 440-459	I00-I15, I26-I28, I30-I41, I44, I45, I51, I52, I70-I99

Second, as some of the CVD outcomes included in the "other diseases of circulatory system" might be relevant to CVD outcomes a less strict definition of CVD incidence was applied by excluding only diseases of veins, lymphatic vessels and lymph nodes as they could be haematological rather than CV outcome.

The rationale for the secondary analysis is that the first non-fatal CVD event might be mild or found by investigations such as ultrasound scan or magnetic resonance imaging. In addition, this group (non-fatal other CVD) includes heterogeneous conditions with uncertain clinical significance. Therefore, it was decided to restrict the secondary analysis to what are assumed to be more severe CVD events with clinical manifestation. Based on this stricter/less strict definitions of CVD events, the CVD incidence rates were re-calculated and survival analyses repeated and compared to the primary analysis.

5.7.2.2 Planned sensitivity analysis of CVD incidence

There were 22 patients with prevalent CVD at the time of start of RRT. People with existing CVD are more likely to have another (recurrent) CVD event. Therefore, these patients were excluded from the primary analysis (Figure 36). To test the effect of this group these 22 patients were included in the sensitivity analysis and survival analyses

were repeated and compared to the primary analysis. All the associations in the sensitivity analyses were additionally adjusted for a binary variable of history of CVD.

5.8 Definition of exposures

5.8.1 Age at start of RRT

Patients were categorised into the following four age groups: 0-<2 years old, 2-<6 years old, 6-<12 years old and 12-<18 years old. These age categories were chosen to be consistent with those used in the ESPN/ERA-EDTA studies to facilitate comparisons.

5.8.2 PRD

PRD was classified according to the ERA-EDTA coding system. In the current analyses CAKUT and GN are used as separate categories. Cystic kidney disease, hereditary nephropathy, ischaemic renal failure, haemolytic-uraemic syndrome (HUS), metabolic disorders, vasculitis and miscellaneous are grouped together in the 'Other' category because the numbers are too small to study separate categories.

5.8.3 Initial type of RRT

Initial type of RRT was categorised as HD, PD and pre-emptively transplanted (pre-Tx).

5.8.4 Changes of RRT during follow-up

As many patients receive a kidney transplant after initial treatment with dialysis, RRT patterns over follow-up were classified into four categories: started on HD and not transplanted during follow-up (abbreviated to HD+Tx-), started on PD and not

transplanted during follow-up (PD+Tx-), pre-emptively transplanted (pre-Tx) and transplanted ever after initiation RRT with dialysis (D+Tx+).

5.8.5 Period of initiation of RRT

The period of initiation of RRT was divided into three periods: 1961-1990, 1991-2000 and 2001-2013. Ideally, time periods would have been categorised into similar length periods such as decades, but because relatively few patients initiated RRT in the period 1961-1980, this time period was combined with the following decade to create approximately similar distributions of numbers of patients in each time period.

In the analysis of CVD incidence the period of initiation of RRT was divided into: 1981-1990, 1991-2000 and 2001-2013.

5.9 Statistical analysis

5.9.1 Descriptive analyses

Demographic, clinical characteristics and types of CVD event were described as proportions for categorical variables. Continuous variables that are normally distributed were described as mean and SD, while median and IQR was used when the distribution was skewed. Differences in distribution of PRD and type of RRT by age at start of RRT and sex were tested by Chi square tests. When more than 20% of the expected numbers were less than 5 for comparisons of proportions, Fisher`s exact test was used. A significance level of 0.05 was used in all statistical tests.

5.9.2 Survival/mortality and CVD incidence analyses

Crude all-cause mortality and CVD incidence rates were calculated per 100 p/y of follow-up for all patients and stratified by: age at start of RRT; sex; PRD; type of RRT; and period of initiation of RRT.

Survival was calculated as proportion of people with the relevant amount of follow-up time who were alive at 10 years and 20 years. The Kaplan-Meier method was used to describe survival for each subgroup, with differences between groups assessed using the log rank test.

Cox proportional hazard models were used to examine the association of age at initiation of RRT, sex, PRD, type of RRT and period of initiation of RRT with all-cause mortality/CVD incidence. The proportional hazard assumption was evaluated graphically using log minus log plots (Appendix 1, Figures 4-8, page 368). The log minus log plots should result in approximately parallel curves if the proportional assumption is not violated. Reference groups for age, sex, PRD, initial type of RRT and period of start of RRT were the groups of patients with the lowest risk of all-cause mortality/CVD incidence based on the reviewed literature and the reference group for RRT during follow-up was the group with the largest number of patients, as follows:

- For age: patients in the oldest age group (12-<18 years of age)
- For sex: females
- For PRD: patients with CAKUT
- For initial type of RRT: pre-emptively transplanted patients
- For RRT during follow-up: patients in the D+Tx+ group

- For calendar period: patients who started RRT in the most recent period (2001-2013)

Crude and adjusted models in the Cox regression analysis are based on the sub-group of patients with complete data (see Figure 36). Characteristics of patients with missing data versus complete data were compared.

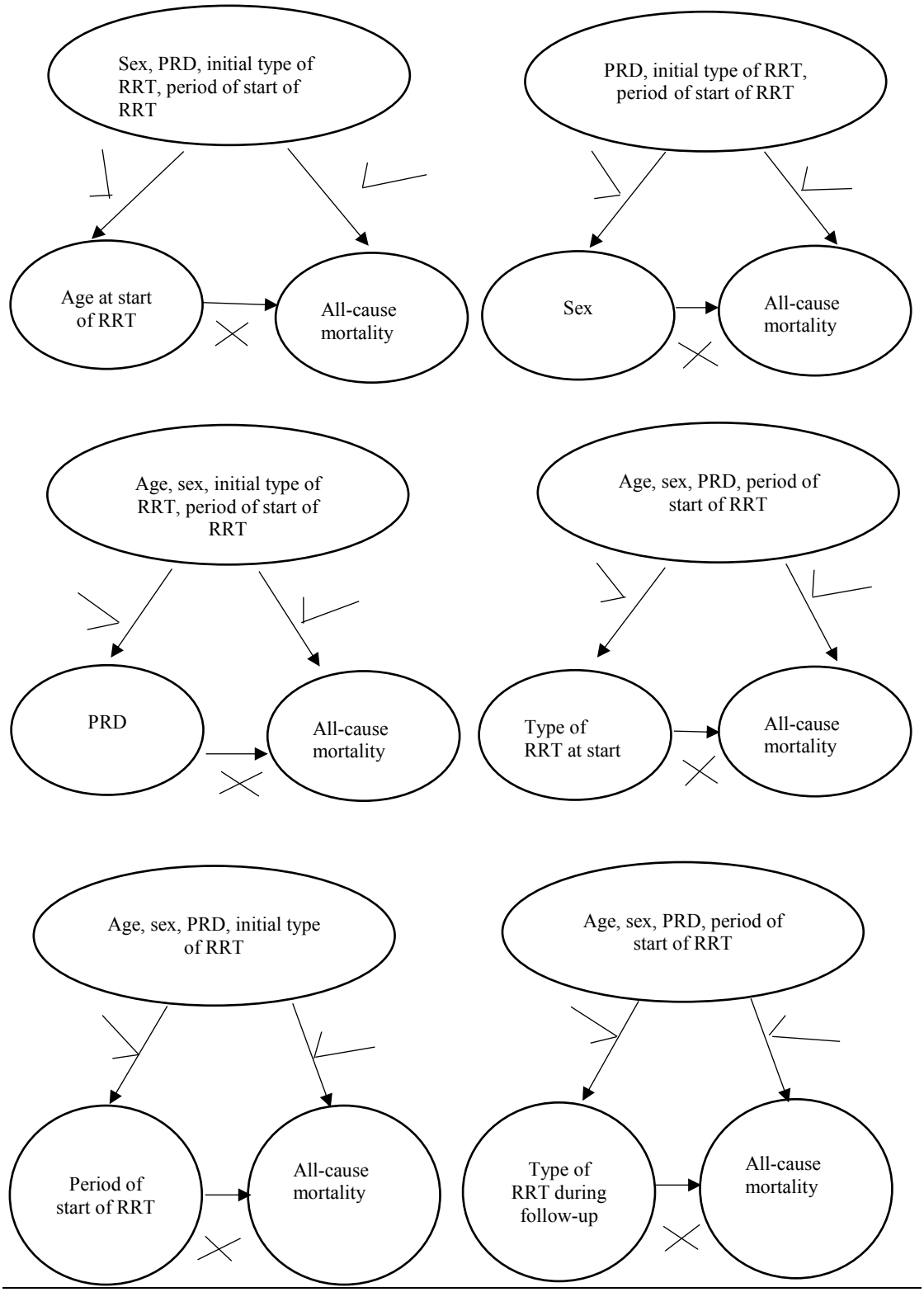
The associations were corrected for confounding factors including age at start of RRT, sex, initial type of RRT and period of start of RRT. These variables were chosen as potential confounding factors based on previous literature that found them to be associated with both exposures and risk of all-cause mortality. Figure 39 schematically depicts the approach taken to adjust for appropriate confounding factors, where tick means that the confounding factor is associated with the exposure and with the outcome, while cross means that the confounding is not on the causal pathway of this association.

The association of sex with all-cause mortality was not adjusted for age at start of RRT because there was no association between sex and age at start of RRT. When a variable is not associated with the exposure but is associated with outcome it is considered as another risk factor and should not be adjusted for (117).

The initial type of RRT might be on the causal pathway in the associations of PRD, age at start of RRT and period of start of RRT with all-cause mortality as the choice of treatment might depend on these factors. The reason for adjusting for a variable that may lie on the causal pathway was to study the effect of the mentioned exposures on the outcome independently from the initial type of RRT. However, by adjusting for

the variable that is on the causal pathway the intermediate effect that goes through this variable is removed (117).

Figure 39. Schematic overview of adjusting for potential confounding factors the associations between age at start of RRT, sex, PRD, type of RRT and period of start of RRT with all-cause mortality



5.9.3 One and five-year all-cause mortality/CVD incidence

In order to compare mortality/CVD incidence across time periods standard follow-up periods of one and five years were applied. One year follow-up data were available for all children. However, only patients who started RRT from 1961 to 2010 and from 1981 to 2010 were included in the analyses of five-year mortality/CVD incidence, respectively, in order to allow all patients to have the opportunity for five-years of follow-up.

5.10 Checklist for reporting the SRR study

This study was reported following the EQATOR collaboration (RECORD) guidelines for observational studies using routinely collected health data. The checklist is presented in Appendix 1 page 376.

The next two chapters present results from the SRR analyses. In particular, Chapter 6 describes characteristics of patients registered in the SRR who started RRT in childhood between 1961 and 2013, their mortality and the association of age at start of RRT, sex, PRD, type of RT and period of start of RRT with all-cause mortality. Chapter 7 describes CVD incidence and its association with age at start of RRT, sex, PRD, type of RT and period of start of RRT in patients who initiated RRT between 1981 and 2013.

Chapter 6. All-cause mortality and causes of death in patients who initiated renal replacement therapy in childhood in Scotland between 1961 and 2013; an analysis of Scottish Renal Registry data

6.1 Results

6.1.1 Characteristics of patients who initiated RRT in childhood

Between 1961 and 2013, 479 children <18 years of age were recorded as starting RRT in Scotland. The characteristics of the total cohort are presented in the first two columns of Table 29. Over half of the patients started RRT when they were older than 12 years of age. There was a higher proportion of boys than girls. CAKUT accounted for almost half of the underlying PRD with the next two most common causes being GN and cystic kidney disease. Almost 90% of patients started RRT by receiving dialysis. There was a slightly higher proportion of patients initiating RRT with HD than by PD.

Table 29 presents the cohort characteristics by period of initiation of RRT. The proportion of boys increased over time. The proportion of patients who started RRT from zero to five years old increased in 1991-2000 compared to 1961-1990 and decreased slightly in 2001-2013 compared to 1991-2000. The proportion of patients with GN decreased in 1991-2000 compared to 1961-1990 and increased slightly in 2001-2013 compared to 1991-2000. The proportion of patients who received HD as the first type of RRT decreased in 1991-2000 compared to 1961-1990 and slightly increased in 2001-2013 compared to 1991-2000. The proportion of patients who started on PD increased in 1991-2000 compared to 1961-1990 and slightly decreased

in 2001-2013 compared to 1991-2000, while the proportion of pre-emptively transplanted patients increased over time.

Table 31. Characteristics of patients who initiated RRT<18 years old in the period from 1961 to 2013 in Scotland

	Total	1961-1990	1991-2000	2001-2013
Characteristics	N (%)	N (%)	N (%)	N (%)
All patients	479	214	133	130
Sex*				
Male	265 (55.3)	107 (50.0)	74 (55.6)	83 (63.8)
Age at start of RRT (years)*				
0-<2	30 (6.3)	9 (4.2)	12 (9.0)	9 (6.9)
2-<6	50 (10.4)	12 (5.6)	23 (17.3)	15 (11.5)
6-<12	113 (23.6)	49 (22.9)	32 (24.1)	32 (24.6)
12-<18	284 (59.3)	144 (67.3)	66 (49.6)	74 (56.9)
missing	2 (0.4)	-	-	-
PRD				
CAKUT	231 (48.2)	103 (48.1)	60 (45.1)	66 (50.8)
GN	80 (16.7)	41 (19.2)	18 (13.5)	21 (16.2)
Other	140 (29.3)	57 (26.6)	46 (34.6)	37 (28.5)
Unknown/missing	28 (5.8)	13 (6.1)	9 (6.8)	6 (4.5)
Initial type of RRT*				
HD	220 (45.9)	138 (64.5)	37 (27.8)	45 (34.6)
PD	207 (43.2)	66 (30.8)	79 (59.4)	62 (47.7)
Tx	50 (10.4)	10 (4.7)	17 (12.8)	23 (17.7)
Unknown/missing	2 (0.4)	-	-	-

PRD-primary renal disease, CAKUT-congenital anomalies of kidney and urinary tract, GN-glomerulonephritis, RRT-renal replacement therapy, HD-haemodialysis, PD-peritoneal dialysis, Tx-transplanted, *p<0.05. Two patients with missing start date of RRT were excluded from the stratified analysis (N=477).

The characteristics of the 30 patients who were excluded from the Cox regression analysis due to missing data compared to patients with complete data is presented in Table 30. There were higher proportions of females and older patients (12-<18 years old) and a lower proportion of pre-emptively transplanted patients among patients with missing data compared to cohort with complete data.

Table 32. Characteristics of patients with complete data and with missing data

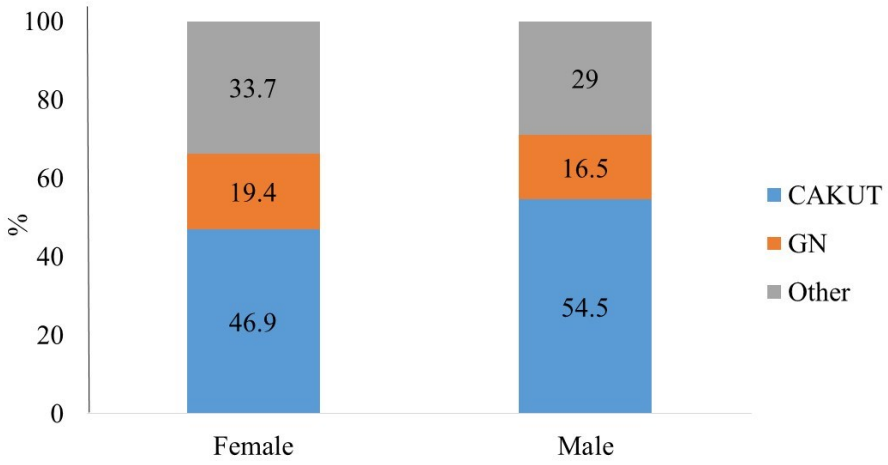
	With complete data	With missing data
Characteristics	N (%)	N (%)
All patients	449	30
Sex		
Male	254 (56.6)	12 (40.0)
Age at start of RRT (years)		
0-<2	29 (6.5)	1 (3.3)
2-<6	49 (10.9)	1 (3.3)
6-<12	111 (24.7)	2 (6.7)
12-<18	260 (57.9)	24 (80.0)
PRD		
CAKUT	229 (51.0)	2 (6.6)
GN	80 (17.8)	-
Other	140 (31.2)	-
Initial type of RRT		
HD	206 (45.9)	14 (46.7)
PD	194 (43.2)	13 (43.3)
Pre-Tx	49 (10.9)	1 (3.3)
Period of start of RRT		
1961-1990	201 (44.7)	13 (43.3)
1991-2000	124 (27.6)	9 (30.0)
2001-2013	124 (27.6)	6 (20.0)
N of deaths	119 (26.5)	7 (23.3)

PRD-primary renal disease, GN-glomerulonephritis, RRT-renal replacement therapy, HD-haemodialysis, PD-peritoneal dialysis, Tx-transplanted, pre-Tx-pre-emptive transplantation.

6.1.2 Distribution of primary renal disease by sex and age at start of RRT

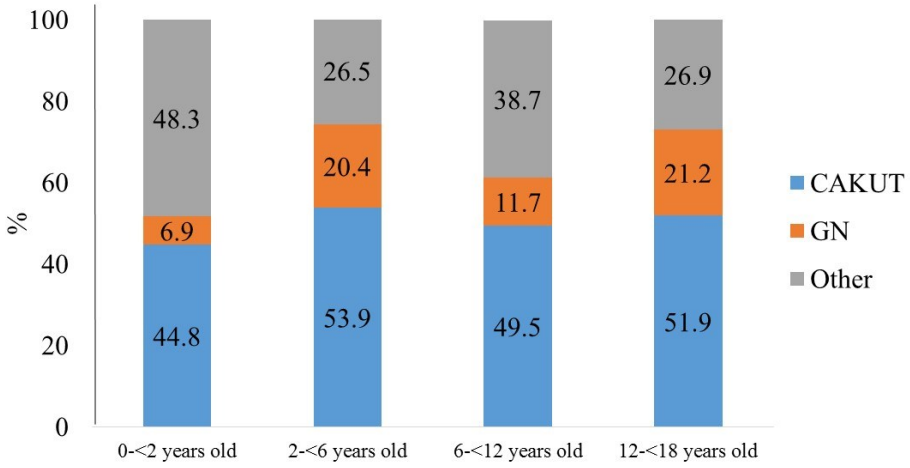
There was no statistically significant difference in distribution of PRD by sex (Figure 40). However, the distribution of PRD significantly differed by age at start of RRT. Figure 41 shows that PRD other than CAKUT and GN formed the largest sub-group among the youngest age category. CAKUT was the largest category of PRD in all age groups older than two years old. GN was more common among patients older than two years old compared to the youngest patients.

Figure 40. Distribution of underlying PRD stratified by sex



CAKUT-congenital anomalies of kidney and urinary tract, GN-glomerulonephritis
differences between groups p=0.28

Figure 41. Distribution of underlying PRD stratified by age at start of RRT

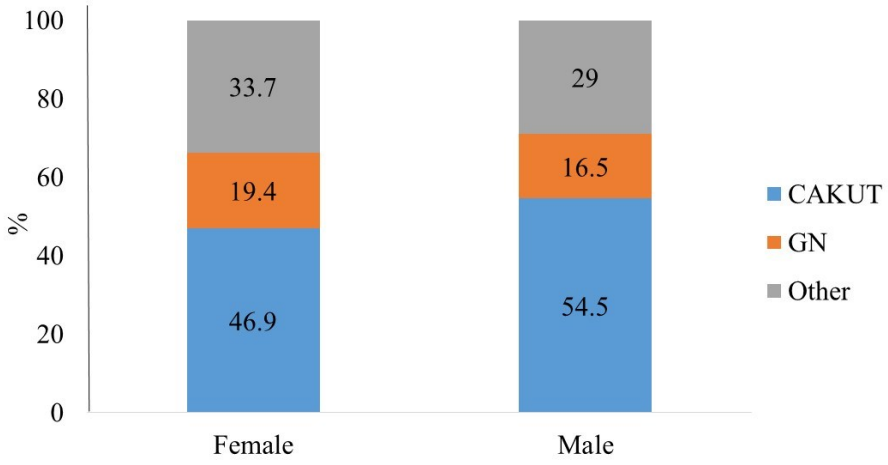


CAKUT-congenital anomalies of kidney and urinary tract, GN-glomerulonephritis
differences between groups p=0.04

6.1.3 Distribution of initial type of RRT by sex and age at start of RRT

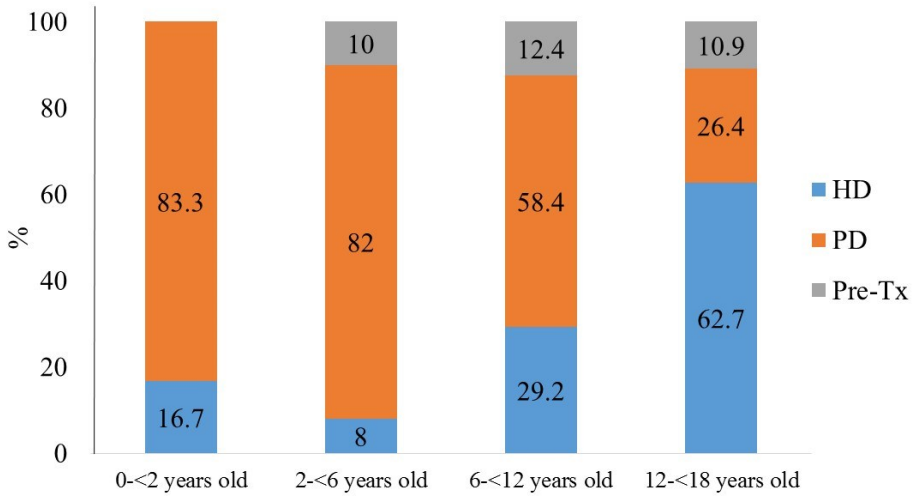
There was no statistically significant difference in distribution of initial type of RRT by sex (Figure 42). However, the distribution of first RRT type significantly differed by age (Figure 43). The proportion of patients who received PD as the first RRT type decreased with age, whereas the proportion of those who started with HD increased with age. There were no patients who received pre-emptive kidney transplantation in the youngest age group.

Figure 42. Distribution of initial type of RRT stratified by sex



CAKUT-congenital anomalies of kidney and urinary tract, GN-glomerulonephritis
differences between groups p=0.28

Figure 43. Distribution of initial RRT modality stratified by age at start of RRT



HD-haemodialysis, PD-peritoneal dialysis, pre-TX-pre-emptive transplantation
differences between groups p<0.0005

6.1.4 First switch of RRT

The majority (N=410) of patients switched RRT type at least once over the follow-up period. The first switch is depicted in Figure 44. The most frequent first RRT changes

were from HD to transplantation and from PD to transplantation. The switch from one dialysis type to the other was less common, while the transition from transplant to dialysis was very rare as was expected. Patients who received their first transplant following a period on dialysis spent a median time of 1.4 (IQR 0.7-2.8) years on dialysis. Patients who started RRT less than two years old had the longest time to their first transplant compared to older patients (Table 31).

Figure 44. First switch of type of RRT

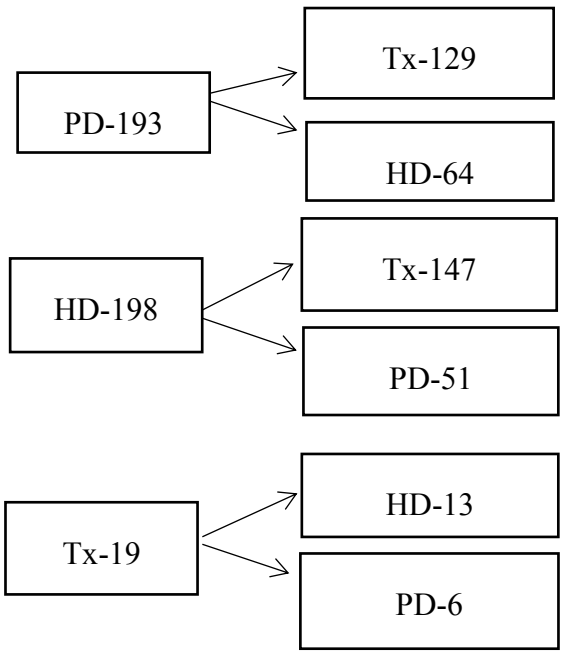


Table 33. Time on dialysis to first transplant stratified by age at start of RRT for the sub-group of patients who received dialysis as their first treatment and subsequently received a transplant

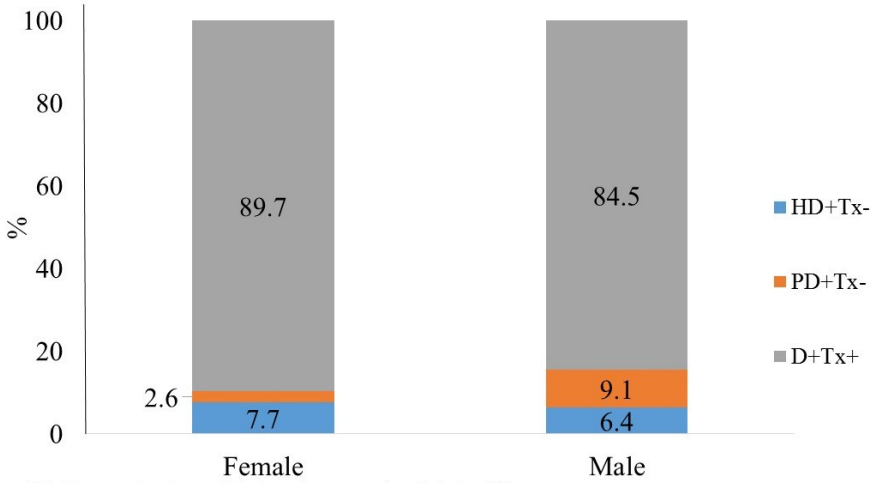
Age at start of RRT (years)	**N**	**Time on dialysis in years to first transplant Median (IQR)**
0-<2	17	2.7 (1.3-4.4)
2-<6	40	1.8 (0.8-3.4)
6-<12	86	1.3 (0.7-3.2)
12-<18	227	1.3 (0.6-2.3)

RRT-renal replacement therapy, IQR-interquartile range

6.1.5 Type of RRT during follow-up time in patients initiating RRT with dialysis stratified by sex and age at start of RRT

Of the 427 patients initiating RRT with dialysis 371 (86.9%) received a kidney transplant after a period of dialysis (abbreviated to D+Tx+). The proportion of those who received a kidney transplant following a period on dialysis was slightly higher among females compared to males (Figure 45) and among older patients compared to the youngest patients (Figure 46).

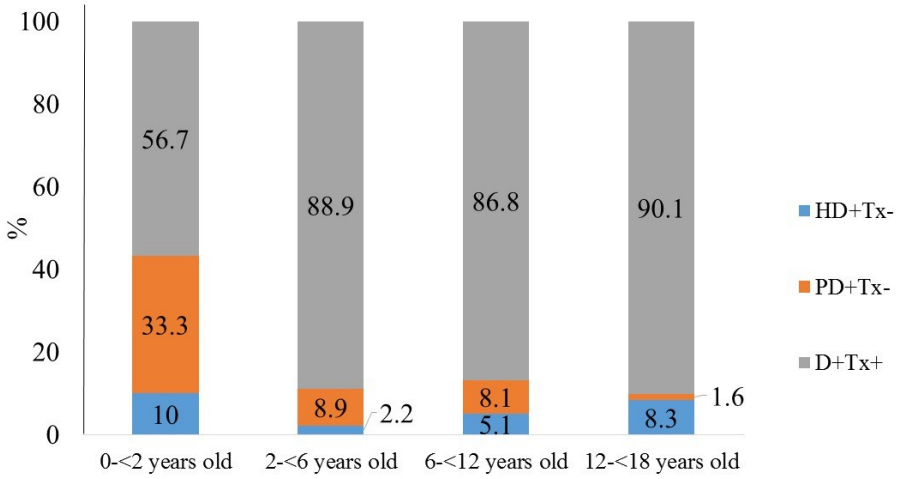
Figure 45. Type of RRT during follow-up stratified by sex in patients who initiated RRT with dialysis



HD+Tx- started on haemodialysis and not transplanted during follow-up
PD+Tx- started on peritoneal dialysis and not transplanted during follow-up
D+Tx+ transplanted ever after starting RRT with dialysis

difference between groups p=0.02

Figure 46. Type of RRT during follow-up in patients initiating RRT with dialysis stratified by age at start of RRT



HD+Tx- started on haemodialysis and not transplanted during follow-up
PD+Tx- started on peritoneal dialysis and not transplanted during follow-up
D+Tx+ transplanted ever after starting RRT with dialysis

Differences between groups p<0.005

6.1.6 Survival and all-cause mortality of patients who started RRT in childhood

In total, 479 patients were followed for a median of 18.3 years (IQR 8.7-27.0 years), giving 8,867 p/y of follow-up. During the study period 126 patients died. The overall crude mortality rate was 1.42 per 100 p/y (95% CI 1.17-1.67). The overall survival among patients requiring RRT was 87.3% (95% CI 84.3-90.3) at 10 years and 77.6% (95% CI 73.8-81.3) at 20 years. In the sub-group of patients with complete data 119 patients died during 8,363 p/y. The overall crude mortality rate among patients with complete data was similar to the total cohort and was 1.42 per 100 p/y (95% CI 1.16-1.67).

Table 32 presents crude mortality rates in sub-groups of patients of the total cohort. The youngest patients, males and patients with CAKUT as PRD had the highest mortality rates compared to older patients, females and patients with GN and other PRD, respectively. Within the treatment categories the mortality rate was the highest among patients who started with HD and lowest among those who were pre-emptively transplanted. Patients who started on dialysis and did not receive a transplant during follow-up had higher mortality compared to patients who received a kidney transplant. The differences in mortality were statistically significant among PRD and type of RRT groups.

Table 34. Number of deaths, person-years of follow-up (p/y) and crude mortality rates (MR) for different subgroups of the total cohort

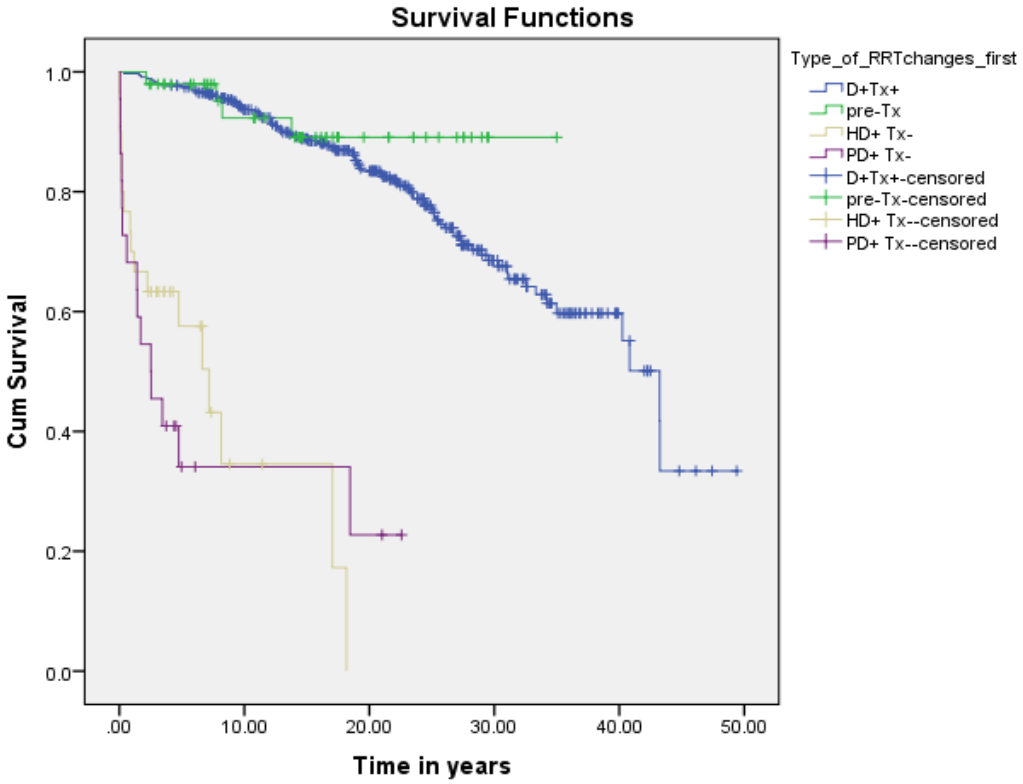
Sub-group characteristics	Number of deaths	p/y	Crude MR per 100 p/y (95% CI)
Age at start of RRT (years)			
0-<2	11	349.2	3.15 (1.32-4.98)
2-<6	10	800.0	1.25 (0.47-2.02)
6-<12	27	2109	1.28 (0.80-1.76)
12-18	77	5620	1.37 (1.16-1.67)
Sex			
Female	56	1600	3.50 (2.59-4.40)
Male	70	1732	4.04 (3.11-4.97)
PRD			
CAKUT	54	1381	3.91 (2.88-4.93)
GN	22	1732	1.27 (0.74-1.79)
Other	44	2340	1.88 (1.32-2.43)
Initial type of RRT			
HD	77	4638	1.66 (1.29-2.03)
PD	44	3464	1.27 (0.89-1.64)
Pre-Tx	4	754.7	0.53 (0.01-1.05)
Type of RRT during follow-up			
HD +Tx-	17	135.0	12.59 (6.99-18.18)
PD+Tx-	17	115.0	14.78 (8.29-21.26)
Pre-Tx	4	754.7	0.53 (0.01-1.05)
D+Tx+	87	7837	1.11 (0.87-1.34)

PRD-primary renal disease, GN-glomerulonephritis, CAKUT-congenital anomalies of kidney and urinary tract, RRT-renal replacement therapy, HD-haemodialysis, PD-peritoneal dialysis, Tx-transplanted, pre-Tx-pre-emptive transplantation, MR-mortality rate, CI-confidence interval, HD+Tx- started on HD and not transplanted during follow-up, PD+Tx- started on PD and not transplanted during follow-up, D+Tx+ transplanted ever after starting on dialysis.

6.1.7. Associations between age at start of RRT, sex, PRD and type of RRT at start and during follow-up with all-cause mortality

Kaplan-Meier survival curves differed significantly by patterns of RRT during follow-up ($p<0.0005$) (Figure 47).

Figure 47. Kaplan-Meier survival curves stratified by patterns of RRT during follow-up



Number at risk

351	284	188	69	12	-	D+Tx+
48	31	14	1	-	-	Pre-Tx
29	3	-	-	-	-	HD+Tx-
21	3	2	-	-	-	PD+Tx-

PD+Tx- started on PD and not transplanted during follow up, HD+Tx- started on HD and not transplanted during follow-up, pre-Tx pre-emptively transplanted, D+Tx+ started on dialysis and received a transplant during follow-up.

Figure 47 shows that patients who started on either form of dialysis and did not receive a kidney transplant over the study period had worse survival compared to those who were pre-emptively transplanted and those who received a kidney transplant after they started RRT with dialysis. Kaplan-Meier survival curves did not differ significantly by age at start of RRT, sex, PRD groups and initial type of RRT.

Table 33 presents results of the associations between age at start of RRT, sex, PRD and type of RRT with all-cause mortality. The youngest patients and patients with PRD other than CAKUT or GN had significantly higher risk of all-cause mortality compared to the oldest patients and patients with CAKUT, respectively. Patients in the HD+Tx- and PD+Tx- groups had significantly higher risk of all-cause mortality compared to patients in the D+Tx+ group. The associations of sex and initial type of RRT with all-cause mortality were not statistically significant.

Table 35. Crude and adjusted hazard ratios for associations between age at start of RRT, sex, PRD and type of RRT with all-cause mortality among children who started RRT in Scotland 1961-2013 with complete data available

Variable	Crude HR (95% CI)	Adjusted HR (95% CI)
Age at start of RRT[a]		
0-1	2.09 (1.07-4.08)	2.50 (1.19-5.25)
2-5	0.85 (0.42-1.71)	1.24 (0.58-2.67)
6-11	0.87 (0.55-1.35)	0.95 (0.59-1.52)
12-<18	1.00	1.00
Sex[b]		
Males	1.30 (0.90-1.88)	1.37 (0.95-1.98)
Females	1.00	1.00
PRD[c]		
GN	0.98 (0.59-1.63)	0.97 (0.58-1.62)
Other	1.54 (1.04-2.31)	1.58 (1.05-2.39)
CAKUT	1.00	1.00
Type of RRT at start[d]		
HD	2.97 (1.08-8.16)	2.64 (0.94-7.38)
PD	2.27 (0.81-6.35)	2.11 (0.74-6.03)
Pre-Tx	1.00	1.00
Type of RRT at follow-up[e]		
HD+Tx-	14.6 (8.11-26.5)	19.4 (10.38-36.37)
PD+Tx-	15.2 (8.43-27.5)	19.5 (9.65-39.56)
Pre-Tx	0.55 (0.20-1.52)	0.65 (0.24-1.78)
D+Tx+	1.00	1.00

PRD-primary renal disease; GN-glomerulonephritis, CAKUT-congenital anomalies of kidney and urinary tract; RRT-renal replacement therapy; HD-haemodialysis; PD-peritoneal dialysis; pre-Tx-pre-emptively transplanted; HD+Tx- started on HD and not transplanted during follow-up, PD+Tx- started on PD and not transplanted during follow-up, D+Tx+ transplanted ever after starting on dialysis. HR-hazard ratio, CI-confidence interval. Only patients with complete data included in unadjusted and adjusted analyses (N=449). N of death=119; Adjusted for [a] sex, PRD, type of RRT at start and period of start of RRT; [b] PRD, type of RRT at start and period of start of RRT; [c]age at start of RRT, sex, type of RRT at start and period of start of RRT; [d] age at start of RRT, sex, PRD and period of start of RRT; [e] age at start of RRT, sex, PRD and period of start of RRT

6.1.8. One-year and five-year all-cause mortality

In total, 18 deaths occurred within the first year after initiation of RRT in the total cohort. Thirty seven deaths occurred in the period of five years from the start of RRT among 450 patients who started RRT from 1961 to 2010. The baseline characteristics of the group with five year follow-up data were similar to the total cohort. In a sub-cohort with complete data 17 and 33 deaths occurred after one and five years from start of RRT, respectively.

Characteristics of patients who died within one and five years after start of RRT in the sub-group of patients with complete data are presented in Table 34. The distribution of deaths within one- and five-years differed significantly by age at start of RRT and type of RRT during follow-up. Patients in the youngest age group and patients who started RRT on dialysis and who did not receive a kidney transplant during follow-up had higher proportions of deaths during these periods compared to older patients and patients who received a kidney transplant after starting on dialysis, respectively. There was no significant difference in the proportion of deaths within one- and five-years by sex and initial type of RRT. The proportion of deaths significantly differed by PRD after five-years from start of RRT, but not after one-year.

Table 35 presents crude and adjusted HRs and 95% CIs for the associations of period of start of RRT with one- and five-year all-cause mortality. One-year mortality was non-significantly higher among patients who initiated RRT in the periods 1961-1990 and 1991-2000 compared to those who started RRT in 2001-2013. Five-year mortality was higher among patients who initiated RRT in the period of 1961-1990 compared to those who started RRT in 2001-2010, but the association was not statistically

significant. Five-year mortality did not differ between patients who started RRT in the period of 1991-2000 compared to 2001-2010.

Table 36. One and five year mortality/survival following start of RRT for sub-groups of patients the sub-group of patients with complete data

Characteristics	**One year after start of RRT**			**Five years after start of RRT**		
	Dead	**Alive**	**p**	**Dead**	**Alive**	**p**
All patients	17	432		33	392	
Age at start of RRT (years)			<0.0005			<0.0005
0-<2	6 (20.7)	23 (79.3)		7 (29.2)	17 (70.8)	
2-<6	3 (6.1)	46 (93.9)		5 (11.1)	40 (88.9)	
6-<12	2 (1.8)	109 (98.2)		8 (7.4)	100 (92.6)	
12-<18	6 (2.3)	254 (97.7)		13 (5.2)	235 (94.8)	
Sex			0.13			0.09
Female	5 (2.6)	190 (97.4)		10 (5.3)	179 (94.7)	
Male	12 (4.7)	242 (95.1)		23 (9.7)	213 (90.3)	
PRD			0.6			0.003
CAKUT	8 (3.5)	221 (96.5)		9 (4.2)	206 (95.8)	
GN	2 (2.5)	78 (97.5)		5 (6.6)	71 (93.4)	
Other	7 (5.0)	133 (95.0)		19 (14.2)	115 (85.8)	
Initial type of RRT			0.3			0.13

Characteristics	One year after start of RRT			Five years after start of RRT		
	Dead	**Alive**	**p**	**Dead**	**Alive**	**p**
HD	10 (4.9)	196 (95.1)		15 (7.7)	181 (92.3)	
PD	7 (3.6)	187 (96.4)		17 (9.1)	169 (90.9)	
Pre-Tx	0	49 (100)		1 (2.3)	42 (97.7)	
Type of RRT during follow-up			<0.0005			<0.0005
HD+Tx-	9 (30.0)	21 (70.0)		12 (54.5)	10 (45.5)	
PD+Tx-	7 (31.8)	15 (68.2)		12 (75.0)	4 (25.0)	
Pre-Tx	0	49 (100)		1 (2.3)	42 (97.7)	
D+Tx+	1 (0.3)	347 (99.7)		8 (2.3)	336 (97.7)	

PRD-primary renal disease, CAKUT-congenital anomalies of kidney and urinary tract, GN-glomerulonephritis, RRT-renal replacement therapy, HD-haemodialysis, PD-peritoneal dialysis, pre-Tx-pre-emptive transplantation. HD+Tx- started on HD and not transplanted during follow-up, PD+Tx- started on PD and not transplanted during follow-up, D+Tx+ transplanted ever after starting on dialysis

Table 37. Crude and adjusted HRs and 95% CI for the association of the period of initiation of RRT with one-year and five-year all-cause mortality after start of RRT

One-year mortality			Five-year mortality		
Period of initiation of RRT	**Crude**	**Adjusted***	**Period of initiation of RRT**	**Crude**	**Adjusted***
	HR (95% CI)	**HR (95% CI)**		**HR (95% CI)**	**HR (95% CI)**
1961-1990	2.06 (0.57-7.52)	3.32 (0.78-14.02)	1961-1990	2.07 (0.78-5.52)	2.53 (0.93-6.94)
1991-2000	1.33 (0.29-5.96)	1.66 (0.33-8.29)	1991-2000	1.31 (0.43-4.01)	0.99 (0.32-3.11)
2001-2013	1	1	2001-2010	1	1

Only patients with complete data were included in unadjusted and adjusted analyses. For one-year mortality: N=449, 17 deaths. For five-year mortality: N=425, 33 deaths. *adjusted for age at start of RRT, sex, PRD and type of RRT at start.

6.1.9 Causes of death for the cohort of patients who started RRT from 1981 to 2013

As mentioned in the methods section the analyses for causes of death only included data from patients who started RRT from 1981 to 2013 and whose data were linked to the national registry of causes of death, resulting in a cohort of 403 patients. Their characteristics were similar to the total cohort. Overall 83 deaths occurred over a total of 6,658 p/y. Median follow up was 16.5 (IQR 7.9-24.5) years. Circulatory disease accounted for 21.7% of all deaths when mentioned as a primary cause of death in death certificates (Table 36). However, when described from any position of death certificates circulatory disease was recorded for 51.2% (N=43) of all deaths. Cerebrovascular disease and cardiac arrest/ arrhythmias followed by ischaemic heart disease were the most common specific types of circulatory disease (Table 37). The main cause of death in the other category was congenital malformations.

Table 38. Numbers and cause-specific mortality rates for primary cause of death derived from death certificates for children who received RRT in Scotland 1981-2013

Cause of death	N (%)	Crude MR per 100 p/y (95% CI)
Circulatory disease	18 (21.7)	0.27 (0.14-0.39)
Infections	4 (4.8)	0.06 (0.001-0.12)
Malignancies	6 (7.2)	0.09 (0.02-0.16)
Renal	32 (38.6)	0.48 (0.31-0.64)
Other	23 (27.7)	0.35 (0.21-0.49)

N-number of deaths, MR-mortality rate, p/y-person years

Table 39. Distribution of different types of circulatory disease derived from any position of the death certificates

Types of circulatory diseases	N (%)
Total	43 (100)
Cerebrovascular disease	8 (18.6)
Cardiac arrest/arrhythmias	8 (18.6)
Ischaemic heart disease	6 (14.0)
Heart failure	4 (9.3)
Cardiomyopathy	2 (4.7)
Other diseases of circulatory system	15 (34.8)

N-number

6.2 Discussion

6.2.1 Summary of findings of the study

The SRR data provided the opportunity to describe characteristics and survival of patients who initiated RRT in childhood in Scotland between 1961 and 2013. Key findings are summarised below followed by comparison with the existing literature and discussion of the strengths and limitations of the work.

This study showed that PRD, initial type of RRT and type of RRT during follow-up differed significantly by age at start of RRT. Distribution of patient characteristics such as age at initiation of RRT, sex and initial type of RRT have also changed over time.

Age at start of RRT, PRD and type of RRT during follow-up were significantly associated with all-cause mortality in patients who initiated RRT in childhood. The associations of sex, initial type of RRT and period of start of RRT with all-cause mortality were not statistically significant.

Circulatory disease was mentioned in any position on just over 50% of death certificates. Cerebrovascular disease and cardiac arrest/arrhythmias were the most common specific types of circulatory disease mentioned on death certificates.

6.2.2 Interpretation of the findings in the context of existing literature

The findings obtained in the current study were generally concordant with the existing literature that are described in details in the following section.

6.2.2.1 Patient characteristics and changes over time

The finding that higher proportions of older patients start on HD, while PD is the most common first RRT modality among younger patients could be explained by the fact that HD for infants is limited due to technical difficulties related to patient size, provision of adequate vascular access, and the need for highly skilled nursing staff (177). As a result, PD is the modality of choice in young children with ESRD. This study has also shown that there were no patients who received a pre-emptive transplantation before two years of age. This is because transplantation is often delayed until the child weights 10 kg or is 2 years old. The primary reason for this delay is that kidney transplantation is technically difficult in very young children (<2 years old) due to the small size of the child compared with the relatively large (usually adult) donor kidney and the small blood vessel calibre of the recipient (177). Van Stralen et al. (169) analysed data from the ESPN/ERA-EDTA, ANZDATA and IPPN registries on patients who started RRT at less than 2 years of age reporting that 91.7% of patients had PD as their initial RRT modality.

The finding of the current study that older patients are more likely to receive a kidney transplant is in line with the data from the ESPN/ERA-EDTA registry (31) which

showed that the probability of children aged 0-4 years receiving a kidney transplant within four years after starting RRT was 35% lower than that of those aged 5-9 years old (HR 0.65, 95% CI 0.57-0.74).

An increase in the proportion of patients who started RRT at a young age over the study period was probably largely due to improved treatment resulted in better survival of young children with CKD prior to the commencement of RRT. This trend was in line with the ANZDATA registry study (118) that also showed that the proportion of young children under five years of age at the start of RRT has increased between 1963 and 2002. The ERA-EDTA registry study (166) showed a similar trend in distribution of patient characteristics between 1985 and 2004. Increasing proportions of pre-emptively transplanted patients over time could be explained by a more proactive policy towards pre-emptive transplantation in children with ESRD (personal communication with Glasgow paediatric nephrologists). In addition, the increase in the number of young children receiving RRT over time, as well as a more frequent use of PD in children in general, has led to a higher proportion of children receiving PD as the first type of RRT.

6.2.2.2 Long-term survival in patients who initiated RRT in childhood

This study reported a crude overall mortality rate of 1.42 per 100 p/y (95% CI 1.17-1.67) over a median of 18.3 years (IQR 8.7-27.0 years) follow-up. This was slightly lower in comparison with the ESPN/ERA-EDTA registry study reporting overall crude mortality rate of 2.0 per 100 p/y over median follow-up of 2.17 years (IQR not reported) (31). This difference might partly be due to a shorter follow-up period in the ESPN/ERA-EDTA study compared to the current study as more deaths occur within a

first year after start of RRT. Furthermore, the inclusion of countries with lower public health expenditure compared to Scotland in the ESPN/ERA-EDTA study (146), however, it is not possible to explore as the ESPN/ERA-EDTA registry does not provide country specific mortality rates.

Ten and 20 year survival reported by the current study were 87.3% (95% CI 84.3-90.3) and 77.6% (95% CI 73.8-81.3) respectively. Only a small number of studies reported the longer-term survival that could be compared with the current results. The Canadian Paediatric ESRD Database study (110) reported a similar 10 year survival of 85.8% (95% CI 82.8-88.8). However, the ANZDATA registry study (118) reported slightly lower 10 and 20 years survival of 78% (95% CI 76-80) and 66% (95% CI 63-69), respectively. This difference may in part be explained by the earlier time period of RRT initiation in the latter study (1963 to 2002) because mortality has probably declined over time.

6.2.2.3 Association of age at start of RRT, type of RRT and PRD with all-cause mortality

The current study has found that the youngest patients had higher risk of all-cause mortality compared to older patients. This finding might be affected by survival bias because of delayed kidney transplantation in patients younger than two years old and not all of these patients survive until they receive a kidney transplant. This finding was in line with the ESPN/ERA-EDTA study (31). The authors showed that the youngest age group (0-4 years old) had the poorest 4 year survival rate, with a HR 4.4 (95% CI 2.8-7.0) for all-cause mortality compared to the oldest age group (15-19 years old). Similarly, data from the ANZDATA registry (118) showed that patients who initiated

RRT at less than 1 year of age had 3.7 times higher risk of all-cause mortality compared to 15-19 year olds over median follow-up of 9.7 years (IQR 4.1-17.6).

The finding that patients who started on dialysis and did not receive a kidney transplant over the study period had a higher risk of all-cause mortality compared to those who received a kidney transplant following period on dialysis might be due to survival bias as healthier patients are more likely to receive a kidney transplant, while patients with comorbidities, some of which may be associated with increased risk of mortality (157), remain on dialysis (178). Observational studies are the main source of evidence showing that successful kidney transplantation increases quality of life and survival as compared with long-term dialysis treatment (29, 31, 118). The ANZDATA registry study (118) and the USRDS study (163) showed that receiving dialysis rather than a kidney transplantation was associated with increased risk of all-cause mortality. Similarly, survival comparison by dialysis modality (HD versus PD) can only be conducted in observational studies as conducting a RCT in this population is extremely difficult. An example of this is the RCT that aimed to compare the survival and quality of life between HD and PD among adult incident dialysis patients in the Netherlands (179). The main limitation of this RCT was low incidence and low response rate. The vast majority of patients refused to participate because of a preference for one of the modalities. After an inclusion period of more than 3 years, only 38 patients had been randomised. Since no dramatic changes in the inclusion rate were expected the steering group decided to stop recruitment as an extension with another 5 to 6 years was not considered to be feasible. Although the RCT was underpowered, the authors reported that after 5 years of follow-up patients who started with HD had a higher risk of all-cause mortality as compared with patients started with PD, HR 3.8 (95% CI 1.1-12.6).

The authors also concluded that observational studies are needed for comparison of both modalities in a larger number of patients (179).

The current study showed that patients with PRD other than GN or CAKUT had higher risk of all-cause mortality compared to patients with CAKUT. This finding may in part be explained by the fact that the group of 'other' types of PRD included diagnoses that cause damage in multiple organs, such as heart, brain and kidneys. For example, the group of vasculitic disorders includes diagnoses such as Wegener's granulomatosis, polyarteritis nodosa, lupus erythematosus, Henoch-Schonlein purpura, and systemic sclerosis (scleroderma). These are systemic disorders that involve inflammation and damage of small- and medium-size vessels in multiple organs. Other diagnoses included in the group of other PRD are Henoch-Schonlein purpura (Immunoglobulin A vasculitis) and (HUS). Both are types of PRD that are characterised by thrombophilia (activation of coagulation system) causing endothelial damage of internal organs (180, 181). Therefore, the observed multi morbidity in patients included in the category of other PRD might contribute to their higher risk of mortality. The Dutch study (29) showed that patients with PRD affecting other vital organs (oxalosis, Goodpasture's syndrome, cystinosis or autosomal recessive cystic disease) had a crude RR 2.4 (95% CI 1.1-5.1) of all-cause mortality compared to patients with other causes of PRD.

This study did not find an association between period of start of RRT and all-cause mortality. Improved health care is expected to result in better survival in recent periods, however, this may be offset by the increasing proportion of younger patients over time that may have resulted in worse survival in recent periods. In contrast to this study the USRDS registry (120) study on patients who initiated RRT on dialysis at

younger than 21 years between 1990 and 2010 showed that each 5-year increment in calendar year of dialysis initiation was associated with a higher risk of all-cause mortality. Adjusted HR for mortality for each 5-year increment among children younger than 5 years at initiation were 0.80 (95% CI, 0.75-0.85) and 0.88 (95% CI, 0.85-0.92) among those 5 years and older. The authors of this study did not suggest an explanation for this finding.

6.2.2.4 Cause of death

The most common cause of death in children who started RRT in Scotland 1981-2013 was renal disease. Circulatory diseases accounted for 21.7% of all deaths when cause of death was identified from primary position on death certificates. Circulatory diseases were mentioned in any position of the death certificates in 51.8% of all deaths. The ESPN/ERA-EDTA registry reported a similar proportion of CV death to this study of 23.0% when described as a primary cause of death. However, cause of death was missing for 41% of deaths in the ESPN/ERA-EDTA study (31). The authors might have underestimated CV mortality if there were a larger proportion of CV deaths among patients with missing data. However, it is unlikely that a large underestimation occurred as missing data on cause of death is probably likely to be random.

6.2.3 Limitations of the study

This study had several limitations which are described in the following paragraphs.

6.2.3.1 Role of chance

As ESRD is rare in children and young adults the sample size of this study is small and small numbers of events precluded stratified analysis. For example, it was not

possible to describe whether cause of death differs between young and older patients. Furthermore, the small sample size may have resulted in a low statistical power of the study which reduces precision of estimates and is reflected in wide 95% CI. Therefore, it was not possible to detect clinically relevant differences. For example, this study did not show a statistically significant association between initial type of RRT and all-cause mortality. In contrast, the ESPN/ERA/EDTA registry showed that patients who initiated RRT with HD or PD had a higher risk of all-cause mortality compared to patients who were pre-emptively transplanted, HR 6.6 (95% CI 2.9-15.2) and 6.5 (95% CI 2.9-14.9), respectively (31). The small number of one- and five-year deaths among the small study population precluded derivation of any meaningful conclusions about improved survival over time. The USRDS registry (120) study reporting improved survival during their study period included a much bigger sample size of 23,401 patients.

It was also not possible to split the "other" category of PRD in to more specific diagnoses due to small numbers within each category. Therefore, it was decided to separate the two biggest PRD categories CAKUT and GN and combine the rest into one broad category. However, such an approach does not allow me to investigate effects of other PRD.

6.2.3.2 Missing data

Another limitation is related to missing data in the SRR. Patients with missing data were excluded from the analyses. This study showed that there were more older patients among excluded compared to the complete cohort which might have resulted

in biased study population. Older patients are more likely to receive a kidney transplant, therefore, have better survival. Exclusion of patients with better survival might have resulted in mortality being overestimated. However, the proportion of excluded patients was very small (6.3%), therefore, it is unlikely that a large overestimation occurred.

Cause of death was not available for all patients in the SRR, therefore, the data were linked with the registry of causes of death. The data on cause of death was only available from 1981, so only patients who started RRT from 1981 to 2013 were included for this part of the analyses. Even though their characteristics were similar to the total cohort I expect that mortality rate for CV death would be higher among patients who started RRT from 1961 to 1980 compared to the included sub-cohort due to improvement of dialysis techniques, better availability of kidney transplantation and increased awareness of the burden of CVD in renal patients among physicians that may have resulted in better survival in recent years compared to earlier years.

Race/ethnicity was missing in the majority of patients, as a result potential racial or ethnic differences in survival could not be explored. The USRDS registry study (163) showed that black patients had a higher risk of all-cause mortality compared to white patients. According to the data from the 2011 census published in the national Records of Scotland website 96.0% of the population in Scotland is white. The numbers of children from non-white ethnic groups is small and there would have been extremely limited power to explore racial/ethnic differences in outcomes.

6.2.3.3 Misclassification of causes of death

Similarly to the ESPN/ERA-EDTA analyses, there is a potential for overestimation of CV mortality when obtained from death certificates (156). See Chapter 3, page 187 for more details.

6.2.3.4 Unrecorded confounding factors

Again, similarly to the ESPN/ERA-EDTA analyses (Chapter 3) it was impossible to assess effect of co-morbidity on mortality as this information was also lacking in the SRR (see page 187 for more details).

6.2.4 Strengths of the study

Despite the limitations, to my knowledge, this is the first study with the longest follow-up period among available studies in Europe that has described changes of characteristics of the population over time, survival, all-cause mortality and cause of death in patients who started RRT in childhood. This study included both dialysis and transplanted patients as well as patients from 0 to 18 years old at start of RRT and was able to compare the risk of death between sub-groups of patients. These factors also improve generalisability of the results. In contrast, previous studies included a selected RRT population and generally only were based on short-term follow-up.

Another major strength of this study is data linkage. This study described cause of death in a sub-cohort with complete data on causes of death due to the ability to link SRR data with the national registry of causes of death.

6.2.5 Generalisability of the study findings

This study included almost all patients receiving RRT in Scotland due to national coverage of the SRR and a very small proportion was excluded because of missing data. This study might potentially miss deaths that occurred outside of Scotland. However, it is unlikely that patients with ESRD receiving dialysis would travel, meaning that such loss to follow-up is unlikely. Therefore, the results obtained in this study could be considered representative of the entire population of patients who initiated RRT from 0 to <18 years of age in Scotland during the study period.

6.2.6 Future research

Future observational cohort studies are needed that include a bigger sample size compared to the current study, perhaps, combining data from several national registries to achieve a sufficient statistical power to be able to overcome the major limitation of this study. Ideally, more complete data is needed to avoid selection bias which could affect obtained results. Detailed discussion of future research is presented in the overall discussion chapter (Chapter 7).

6.2.7 Conclusion

This study demonstrates that the characteristics and treatment history of patients who started RRT in childhood have changed in the period from 1961 and 2013. CVD accounted for 51.8% of all deaths that occurred in patients who started RRT between 1981 and 2013. Young age at start of RRT, PRD other than CAKUT or GN and receiving dialysis was associated with a higher risk of all-cause mortality compared to older patients, patients with CAKUT and receiving a kidney transplantation, respectively.

This study suggests that CVD is common among children who receive RRT. Therefore, further information is required about CVD incidence and risk factors associated with development of CVD after start of RRT in childhood. The next Chapter presents the analyses of the SRR data linked with CV hospital admissions describing CVD incidence and the association of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with CVD in patients who initiated RRT in childhood in Scotland.

Chapter 7. Cardiovascular disease incidence among patients who initiated RRT in childhood in Scotland between 1981 and 2013: an analysis of the Scottish Renal Registry linked to causes of death and cardiovascular hospital admissions

7.1 Results

7.1.1 Characteristics of patients who started RRT in childhood from 1981 to 2013 in Scotland

In total 381 patients without existing CVD started RRT before the age of 18 years between 1981 and 2013 in Scotland. Their characteristics are similar to the total cohort described in Chapter 5. Characteristics of patients with complete and missing data are presented in Table 40. Patients with missing data were older and there were slightly more females than males compared to patients with complete data. Furthermore, patients with missing data in comparison to patients with complete data were less likely to be pre-emptively transplanted.

Table 40. Characteristics of patients with complete data and with missing data who started RRT between 1981 and 2013 in Scotland

Characteristics	Patients with complete data N (%)	Patients with missing PRD N (%)
All patients	356	25
Age at start of RRT (years)		
0- <2	28 (7.9)	1 (4.0)
2- <6	46 (12.9)	1 (4.0)
6- <12	88 (24.7)	2 (8.0)
12- <18	194 (54.5)	21(84.0)
Sex		
Male	209 (58.7)	9 (36.0)
PRD		
CAKUT	185 (52.0)	-
GN	59 (16.6)	-
Other	112 (31.5)	-
Initial type of RRT		
HD	143 (40.2)	12 (48.0)
PD	168 (47.2)	12 (48.0)
Pre-Tx	45 (12.6)	1 (4.0)

PRD-primary renal disease, GN-glomerulonephritis, RRT-renal replacement therapy, HD-haemodialysis, PD-peritoneal dialysis, Tx- transplanted, Pre-Tx-pre-emptively transplanted. % refers to column %

7.1.2 CVD incidence in patients who started RRT in childhood in Scotland 1981-2013

In total, 381 patients were followed for a median of 12.9 (IQR 5.6-21.5) years, giving 5,223 p/y of follow-up. During follow-up 134 (35.2%) patients developed CVD identified using the broad definition. Mean age at CVD incidence was 21.5 years (SD 9.5). The majority of patients with CVD had a non-fatal CVD event as their first event (N=120), while a fatal CVD event was the first CVD event for 14 patients. In the sub-group of patients with complete data 128 patients developed CVD during 4,909 p/y. The overall crude CVD incidence was 2.6 (95% CI 2.2-3.0) and 1.9 (95% CI 0.4-3.4) among patients with complete and incomplete data, respectively. Table 41 presents the crude CVD incidence rates for sub-groups of patients with complete data. The differences in all sub-groups were not statistically significant, as indicated by overlapping 95% CIs in all sub-groups.

The most common types of first CVD event were other diseases of the circulatory system accounting for 62.7% of the CVD events, followed by cerebrovascular disease and heart failure (Figure 48). Among the groups of other diseases of the circulatory system ('other' group in Figure 48) the most common form was other forms of heart disease (29.7%) (Table 42). Within the latter group valvular heart disease (41.4%) and cardiomegaly (38.0%) were the most common types of CVD, while pericarditis accounted for 20.2% of cases.

Table 41. CVD incidence rate in sub-group of patients who started RRT between 1981 and 2013 in Scotland

Characteristics	CVD N (%)	Total p/y	CVD incidence rate per 100 p/y (95% CI)
Age at start of RRT			
0-<2	8 (6.0)	285	2.8 (0.9-4.7)
2-<6	14 (10.4)	636	2.2 (1.1-3.3)
6-<12	24 (17.9)	1,360	1.8 (1.1-2.5)
12-18	88 (65.7)	2,941	3.0 (2.4-3.6)
Sex			
Male	79 (59.0)	2,700	2.9 (2.3-3.5)
Female	55 (41.0)	2,523	2.2 (1.6-2.8)
PRD			
CAKUT	65 (48.5)	2,538	2.6 (1.9-3.2)
GN	24 (17.9)	944	2.5 (1.5-3.5)
Other	39 (29.1)	1,426	2.7 (1.8-3.5)
Missing	6 (4.5)	314	1.9 (0.4-3.4)
Therapy modality at start of RRT			
HD	66 (49.3)	2,152	3.1 (2.4-3.8)
PD	56 (41.8)	2,469	2.3 (1.7-2.9)
Tx	12 (9.0)	601	2.0 (0.9-3.1)
Period of start of RRT			
1981-1990	70 (52.2)	2,428	2.9 (2.2-3.6)
1991-2000	40 (29.9)	1,966	2.0 (1.4-2.6)
2001-2013	24 (17.9)	828	2.9 (1.8-4.0)

CVD-cardiovascular disease, PD-peritoneal dialysis, HD-haemodialysis, RRT-renal replacement therapy, p/y-person/years, CI-confidence interval, CAKUT-congenital anomalies of kidney and urinary tract, GN-glomerulonephritis

Figure 48. Distribution of first non-fatal and fatal CVD events (broad definition)

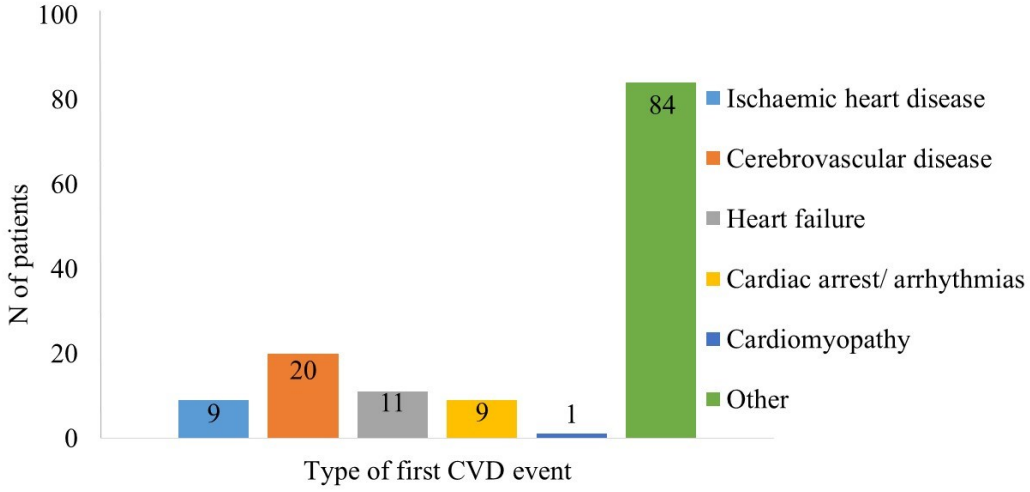
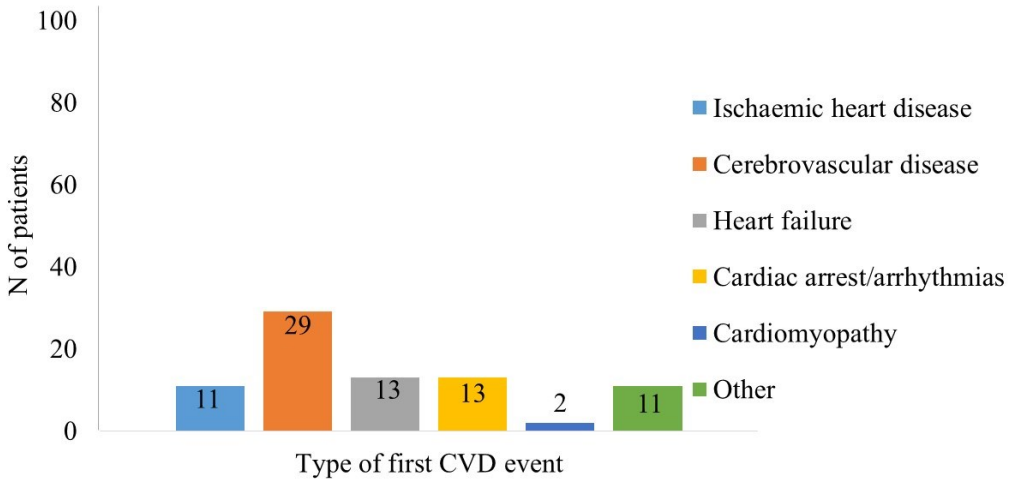


Table 42. Distribution of types of 'other' group in Figure 46 (fatal and non-fatal)

Type of other diseases of the circulatory system	**N**	**(%)**
Other forms of heart disease	25	29.7
Diseases of veins, lymphatic vessels and lymph nodes	23	27.3
Other and unspecified disorders of the circulatory system	14	16.6
Diseases of arteries and arterioles	11	13.3
Hypertensive heart disease	5	5.9
Disease of pulmonary circulation	4	4.8
Chronic rheumatic heart disease	2	2.4
Total	**84**	100

In the secondary analysis there were 80 patients who developed CVD defined using strict definition. Of these CVD events 60 were non-fatal and 20 fatal CVD events. The CVD incidence was 1.4 (95% CI 1.1-1.7) per 100 p/y, which was significantly lower compared to the incidence CVD using the broader definition in the primary analysis. The most common types of CVD events were cerebrovascular disease followed by heart failure, cardiac arrest and arrhythmias (Figure 49). Cardiomegaly (55%) and endocarditis (27%) were the most common fatal types of CVD in the other category.

Figure 49. Distribution of first non-fatal and fatal CV events in the secondary analysis with a "stricter" definition of CVD

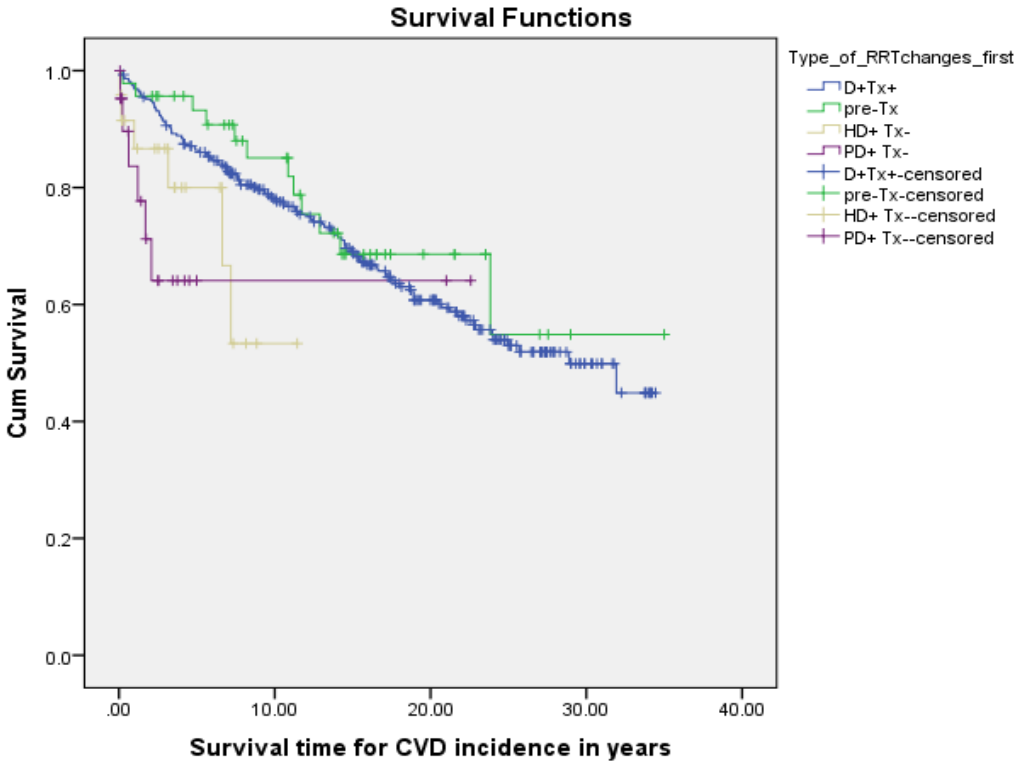


After applying a less strict definition of CVD incidence (only excluding diseases of veins, lymphatic vessels and lymph nodes) 96 patients developed CVD. Of these CVD events 79 were non-fatal and 17 fatal CVD events. The most common CVD types were other diseases of the circulatory system (29.2%), followed by cerebrovascular disease (20.1%) and heart failure (12.3%).

7.1.3 Associations of age at start of RRT, sex PRD and type of RRT with CVD incidence (broader definition)

Kaplan-Meier survival curves differed significantly by RRT modality patterns during follow-up (p=0.04) (Figure 50).

Figure 50. Kaplan-Meier survival curves for CVD incidence among children starting RRT in Scotland stratified by type of RRT during follow-up



Number at risk

260	191	101	17	-	D+Tx+
49	29	9	1	-	Pre-Tx
24	1	-	-	-	HD+Tx-
23	2	2	-	-	PD+Tx-

PD+Tx- started on PD and not transplanted during follow up, HD+Tx- started on HD and not transplanted during follow-up, pre-Tx pre-emptively transplanted, D+Tx+ started on dialysis and received a transplant during follow-up.

Figure 50 shows that patients in the PD+Tx- and HD+Tx- groups were more likely to develop CVD incidence compared to those who were pre-Tx and D+Tx+ (abbreviations are explained below Figure 50). Kaplan-Meier survival curves were similar by age at start of RRT, sex, PRD groups and initial type of RRT.

Table 43 presents crude and adjusted HRs and 95% CIs for the associations between age at start of RRT, sex, PRD and type of RRT at start and RRT modality patterns during follow-up with CVD based on the broader definition. The adjusted analysis showed that patients who started RRT from six to 11 years of age had a significantly lower risk of CVD incidence compared to patients in the oldest age group. Patients in the PD+Tx- group had a significantly higher risk of CVD incidence compared to the D+Tx+ group. Patients in the HD+Tx- had a non-significantly higher risk of CVD compared to patients in the D+Tx+ group. Associations between PRD, type of RRT at start and sex with CVD incidence were not statistically significant.

The secondary analysis with a less strict definition was similar to the primary analysis when a broad definition of CVD incidence was applied. Secondary analysis with a strict definition of CVD incidence showed that patients in the PD+Tx- and HD+Tx- groups had a significantly higher incidence of this definition of CVD compared to the D+Tx+ group. In contrast to the primary analysis, the association of age at start of RRT with more strictly defined CVD incidence was no longer statistically significant. Male patients had a higher risk of CVD compared to females. Patients with PRD other than CAKUT or GN had a significantly higher risk of CVD compared to patients with CAKUT.

Table 43. Crude and adjusted HRs and 95% CIs of the associations between age at start of RRT, sex, PRD and type of RRT with CVD in the primary and secondary analyses based on broader and stricter definition of cardiovascular disease incidence among children who started RRT in Scotland 1981-2013

Variable	Primary analysis (broad CVD definition)*		Secondary analysis (strict CVD definition)**	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age at start of RRT[a]				
0-<2	0.91 (0.44-1.89)	0.95 (0.44-2.05)	0.71 (0.23-1.98)	0.86 (0.29-2.53)
2-<6	0.74 (0.42-1.29)	0.82 (0.44-1.52)	0.54 (0.23-1.26)	0.76 (0.31-1.89)
6-<12	0.59 (0.34-0.94)	0.59 (0.36-0.96)	0.63 (0.35-1.12)	0.72 (0.39-1.31)
12-18	1.00	1.00	1.00	1.00
Sex[b]				
Males	1.26 (0.88-1.80)	1.32 (0.92-1.90)	1.45 (0.90-2.32)	1.69 (1.05-2.74)
Females	1.00	1.00	1.00	1.00
PRD[c]				
GN	1.00 (0.62-1.60)	0.95 (0.59-1.55)	1.16 (0.63-2.18)	1.12 (0.59-2.19)
Other	1.05 (0.71-1.57)	1.14 (0.75-1.71)	1.45 (0.87-2.42)	1.72 (1.02-2.91)
CAKUT	1.00	1.00	1.00	1.00

Variable	Primary analysis (broad CVD definition)*		Secondary analysis (strict CVD definition)**	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Initial type of RRT[d]				
HD	1.54 (0.83-2.87)	1.39 (0.74-2.63)	2.04 (0.86-4.79)	1.44 (0.57-3.61)
PD	1.09 (0.58-2.04)	1.20 (0.63-2.29)	1.14 (0.47-2.76)	1.74 (0.73-4.16)
Pre-Tx	1.00	1.00	1.00	1.00
Type of RRT during follow-up[e]				
PD+Tx-	2.52 (1.02-6.22)	3.32 (1.24-8.88)	4.35 (1.55-12.19)	7.30 (2.30-23.16)
HD+Tx-	2.20 (0.95-5.13)	2.14 (0.87-5.23)	5.55 (2.42-12.76)	8.38 (3.31-21.23)
Pre-Tx	0.82 (0.45-1.49)	0.82 (0.45-1.51)	0.74 (0.32-1.73)	0.74 (0.32-1.73)
D+Tx+	1.00	1.00	1.00	1.00

PRD-primary renal disease; GN-glomerulonephritis, CAKUT-congenital anomalies of kidney and urinary tract; RRT-renal replacement therapy; HD-haemodialysis; PD-peritoneal dialysis; Pre-Tx-pre-emptively transplanted; HR-hazard ratio, CI-confidence interval. PD+Tx- started on PD and not transplanted during follow up, HD+Tx- started on HD and not transplanted during follow-up, D+Tx+ started on dialysis and received a transplant during follow-up. Only patients with complete data included in unadjusted and adjusted analyses (N=356). *CVD events N=128; ** CVD events N=75; Adjusted for [a] sex, PRD, type of RRT at start and period of start of RRT; [b] PRD, type of RRT at start and period of start of RRT; [c] sex, age at start of RRT, RRT at start and period of start of RRT; [d] sex, age at start of RRT, PRD and period of start of RRT; [e] sex, age at start of RRT, PRD and period of start of RRT;

7.1.4 One- and five-year CVD incidence

Fifteen patients developed CVD defined using the broader criteria within the first year after initiation of RRT. Forty-eight patients out of the 335 patients with five-year follow-up and complete data developed CVD within five years after initiation of RRT. Characteristics of patients for whom five-year follow-up was available (i.e. those who started RRT from 1981 to 2010) were similar to the main cohort.

Proportions of patients who developed CVD within one and five years after starting RRT by key characteristics are presented in Table 44. A statistically significantly higher proportion of patients in the PD+Tx- and HD+Tx- groups developed CVD compared to those in the pre-Tx and D+Tx+ groups. No other significant differences between groups were found.

In the secondary analysis with a stricter definition of CVD nine and 23 patients developed CVD within one and five years after start of RRT, respectively. As in the primary analysis higher proportions of patients in the PD+Tx- and HD+Tx- groups developed CVD compared to those who were in the pre-Tx or the D+Tx+ groups.

Cox regression analyses did not show a statistically significant association between period of start of RRT with one-year and five-year CVD incidence (Table 45). However, patients who started RRT in the earliest decade had a lower risk of one-year and five-year CVD defined using the broader definition compared to patients who started RRT in the latest decade. In contrast, the reverse pattern was found in the analysis based on the stricter definition of CVD.

Table 44. Proportions of patients who developed CVD one and five years after starting RRT by key characteristics

	One-year		Five-year	
Characteristics	**CVD+**	**CVD -**	**CVD+**	**CVD -**
All patients	15	341	48	287
Age at start of RRT				
0-<2	2 (7.1)	26 (92.9)	4 (16.7)	20 (83.3)
2-<6	4 (8.7)	42 (91.3)	8 (19.0)	34 (81.0)
6-<12	2 (2.3)	86 (97.7)	9 (10.6)	76 (89.4)
12-18	7 (3.6)	187 (96.4)	27 (14.7)	157 (85.3)
Sex				
Female	5 (3.4)	142 (96.6)	15 (10.6)	126 (89.4)
Male	10 (4.8)	199 (95.2)	33 (17.0)	161 (83.0)
PRD				
CAKUT	9 (4.9)	176 (95.1)	22 (12.7)	151 (87.3)
GN	2 (3.4)	57 (96.6)	10 (18.2)	45 (81.8)
Other	4 (3.6)	108 (96.4)	16 (15.0)	91 (85.0)
Initial type of RRT				
HD	9 (6.3)	134 (93.7)	21 (15.8)	112 (84.2)
PD	5 (3.0)	163 (97.0)	24 (14.9)	137 (85.1)
Pre-Tx	1 (2.2)	44 (97.8)	3 (7.3)	38 (92.7)
Type of RRT during follow-up *				
HD+Tx-	3 (12.5)	21 (87.5)	4 (25.0)	12 (75.0)
PD+Tx-	2 (11.1)	16 (88.9)	4 (30.8)	9 (69.2)
Pre-Tx	1 (2.2)	44 (97.8)	3 (7.3)	38 (92.7)
D+Tx+	9 (3.3)	260 (96.7)	37 (14.0)	228 (86.0)

CAKUT-congenital anomalies of kidney and urinary tract, GN-glomerulonephritis, RRT-renal replacement therapy, HD-haemodialysis, PD-peritoneal dialysis, pre-Tx-pre-emptive transplantation, PD+Tx- started on PD and not transplanted during follow up, HD+Tx- started on HD and not transplanted during follow-up, D+Tx+ started on dialysis and received a transplant during follow-up. CVD-cardiovascular disease. Patients with complete data on PRD are included.*p<0.05

Table 45. Crude and adjusted HRs and 95% CIs for the associations between period of starting RRT with CVD incidence in the primary analysis and secondary analysis based on broader and stricter definition of cardiovascular disease incidence among children who started RRT in Scotland 1981-2013

	Primary analysis (broad definition)*			Secondary analysis (strict definition)*		
Period of RRT	**CVD N**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	**CVD N**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
One year CVD						
1981-1990	3	0.44 (0.11-1.77)	0.38 (0.09-1.57)	3	1.34 (0.22-7.99)	1.49 (0.22-9.79)
1991-2000	6	0.95 (0.31-2.94)	1.11 (0.35-3.57)	4	1.92 (0.35-10.46)	1.85 (0.30-11.43)
2001-2013	6	1.00	1.00	2	1.00	1.00
Five year CVD						
1981-1990	14	0.59 (0.29-1.21)	0.58 (0.28-1.19)	11	1.68 (0.58-4.85)	1.67 (0.56-4.92)
1991-2000	17	0.76 (0.39-1.49)	0.74 (0.27-1.46)	7	1.11 (0.35-3.49)	1.05 (0.33-3.37)
2001-2010	17	1.00	1.00	5	1.00	1.00

Total number of patients include for one year CVD incidence =356. Total N of patients include for five year CVD incidence =335; n- total number of CVD events;

*Broad definition of CVD, **Strict definition of CVD. Adjusted for age at start of RRT, sex, PRD, type of RRT at start; CVD-cardiovascular disease;

RRT-renal replacement therapy; HR-hazard ratio, CI-confidence interval.

7.1.5 Planned sensitivity analysis

Among 22 patients with prevalent CVD the most common CVD diagnoses were other forms of circulatory disease (86%), with the most common type within this category being diseases of veins and arterioles (36%). Cardiomyopathy, ischaemic heart disease and cerebrovascular disease accounted for 4.5% per each category. Sensitivity analysis after inclusion of 22 patients with prevalent CVD showed similar results to the primary analysis. The results of the sensitivity analysis are presented in Appendix 1, Table 9, page 374.

7.2 Discussion

7.2.1 Summary of findings of the study

The SRR data linked with the national registry of CV hospital admissions and causes of death provided an opportunity to fulfil one of the major gaps in current knowledge about CVD incidence in patients who initiated RRT in childhood. This study has shown that over a third of patients developed incident CVD over a median follow-up of 12.9 (IQR 5.6-21.5) years after initiating RRT in childhood in Scotland from 1981 to 2013. The most common category of CVD within the broad definition was other diseases of the circulatory system. Valvular heart disease and cardiomegaly were the most common specific CVD types within this category. When the stricter definition of CVD incidence was applied the most common specific types were cerebrovascular disease, followed by heart failure, cardiac arrest and arrhythmia.

The primary analyses based on the broad definition of CVD showed that age at start of RRT and type of RRT during follow-up were significantly associated with CVD

incidence. Patients who started RRT from six to 11 years of age had a significantly lower risk of CVD incidence compared to patients who started RRT when they were between 12 and 18 years old. Patients in the PD+Tx- group had a significantly higher risk of CVD compared to patients in the D+Tx+ group. Patients in the HD+Tx- group had a non-significantly higher risk of CVD compared to patients in the D+Tx+. Associations between PRD, type of RRT at start, period of start of RRT and sex with CVD incidence were not statistically significant.

The secondary analyses based on the stricter definition of CVD showed slightly different results. Higher risk of CVD compared to patients in the D+Tx+ group was also found among patients in the HD+Tx- group as well as in the PD+Tx- group. Male patients had a significantly higher risk of CVD incidence compared to female patients. Patients with PRD other than CAKUT or GN had a significantly higher risk of CVD incidence compared to patients with CAKUT. In contrast to the primary analyses, the association of age at start of RRT with CVD incidence was no longer statistically significant.

7.2.2 Interpretation of the findings in the context of existing literature

7.2.2.1 Incidence of CVD

According to the literature review described in Chapter 4 there is only one study that used a comparable definition of CVD incidence with the current study (109). This single-centre Canadian study included 418 pre-emptively transplanted patients and patients who received a kidney transplant following a period on dialysis. CVD incidence in this study was defined as first fatal or non-fatal CVD event obtained from hospital admission administrative dataset. The authors reported an incidence of 1.07

per 100 p/y (95% CI not reported) in their study, which was similar to the CVD incidence of the current study among transplanted patients of 1.2 (95% CI 0.8-1.5) per 100 p/y. The follow-up in the Canadian study was approximately half as long (mean 6.4 (SD 5.1) years) as in the current study (mean 13.7 (SD 9.4) years).

7.2.2.2 Types of CVD

The finding of the current study that cardiomegaly was one of the most common types of CVD in the primary analysis could be explained by cardiac remodelling that results from hypertension, volume and sodium overload. This leads to LVH as a response to mechanical or haemodynamic overload (182). Previous research has shown that at initiation of maintenance dialysis 69–82% of paediatric patients have LVH (183).

When the CVD definition was based on stricter criteria the most common type of CVD was cerebrovascular disease. This could be explained by vascular injury, the second key process involved in the development of CVD in patients receiving RRT. Patients receiving RRT experience abnormal mineral metabolism including increased calcium and phosphate ion product or hyperphosphatemia which may be key factors underlying development of coronary artery calcification (CAC). The mechanisms include either stimulation of the uptake and precipitation of calcium and phosphate into the vessel or a decrease of the inhibitory process that prevents these ions from precipitation (184). This finding was in line with the Canadian study that classified CVD events as cerebrovascular accident, myocardial infarction, congestive heart failure and sudden cardiac arrest. The authors reported that cerebrovascular events were the most common type of incident CVD events accounting for 43% of all CVD events in patient who were younger than 18 years old at the time of transplantation (109). The distribution

of CVD types in the Canadian study was similar to the current study, i.e. cerebrovascular disease was the most common and was flowed by heart failure and cardiac arrest. A Dutch study similarly reported that death from cerebrovascular accidents accounted for 41% of all deaths among patients who started RRT in childhood and survived until they were at least 18 years old (29). Another study that reported non-fatal CVD events was a USRDS study including only patients receiving dialysis that limited their analyses to cardiac-related events defined as arrhythmia, cardiac arrest, valvular heart disease and cardiomyopathy. The authors reported that arrhythmia was the most common type of cardiac event (19.6%) followed by cardiomyopathy (9.6%) (164).

7.2.2.3 Association of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with CVD incidence

The literature review presented in Chapter 4 showed that limited knowledge exists about the association of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with CVD outcomes. The available studies mostly used fatal CVD events as the primary outcomes of interest in their analyses. In contrast, the current study used both fatal and non-fatal CVD events. In general, the findings of the associations between potential risk factors with CVD incidence were in line with previous studies reporting only on fatal CVD events. However, different definitions of CVD outcomes made it difficult to directly compare the current findings with previous studies. Ideally, it would be desirable to re-run the analyses using a similar definition of CVD outcome to match the obtained results with the other authors. However, small number of fatal CVD events observed in the current study resulted in insufficient statistical power to identify difference in associations of risk factors with fatal CVD events.

7.2.2.3.1 Association of age at start of RRT with CVD incidence

The primary analysis based on the broader definition of CVD showed that patients who started RRT from six to 11 years of age had a significantly lower risk of CVD incidence compared to patients in the oldest age group (12-18 years old). This finding may be explained by the fact that patients who start RRT in older age live longer compared to those who start RRT in younger age. Therefore, older patients have a higher chance to survive until development of CVD compared to younger patients. Alternatively, this finding might be a chance finding due to multiple testing because after applying a "strict" definition the association was no longer statistically significant. However, there may be limited statistical power due to smaller number of CVD events when using the stricter definition.

The USRDS study including incident paediatric dialysis patients from 1991 to 1996 showed that the proportion of non-fatal cardiac-related incident events was significantly higher in the oldest patients (15-19 years old) compared to younger ones (0-4 years old) (164). In contrast, another study from the USRDS registry using cardiac death as outcome showed no association between age at death and cardiac mortality (185).

7.2.2.3.2 Association of sex with CVD incidence

In the current analysis no association between sex with CVD incidence using the broad definition is found. This is in line with the USRDS registry study that analysed 1,380 deaths from 1990 to 1996 among patients who started RRT as children and died before 30 years of age (185). However, the results of the secondary analysis using stricter definition showed that male patients had a borderline significantly higher incidence of CVD compared to female patients. This was in line with ERA-EDTA study in adult

RRT population showing that female patients have a lower risk of CV mortality compared to men (186). Bearing in mind that these results are borderline significant and might be due to chance this finding should be interpreted with caution.

7.2.2.3.3 Association of PRD with CVD incidence

This study has shown that patients with PRD other than CAKUT and GN had a significantly higher risk of CVD incidence compared to patients with CAKUT. The explanation of this finding is presented in previous Chapter 5, page 265. Briefly, the group of 'other' types of PRD included diagnoses that are characterized by arteriopathies and thrombophilia. Research among children in the general population has shown that the presence of arteriopathies and thrombophilia are associated with increased risk of arterial ischaemic stroke compared to children without these conditions (187). The inflammation and damage of small- and medium-size vessels in many organs, including kidney, heart and brain (180, 181) might contribute to the higher risk of CVD incidence.

The only other study that explored the association of PRD with CVD outcome in children receiving RRT is the USRDS study (185). The authors did not find a statistically significant association between PRD and cardiac mortality.

7.2.2.3.4 Association of type of RRT with CVD incidence

This study has shown that patients in PD+Tx- and HD+Tx- groups had a significantly higher risk of CVD compared to patients in the D+Tx+ group. This finding might be explained by referral bias which has been previously introduced in Chapter 5, page 265 (178). The association between RRT patterns and CVD incidence was in line with the Dutch (29) and the USRDS (185) studies. However, the Canadian study (109) did

not find a statistically significant difference in CVD incidence between transplanted patients who started on dialysis and pre-emptively transplanted patients. The difference might be due to the fact that the Canadian study had a shorter follow-up time compared to the current study and they only analysed type of RRT at the time of initiation, while the current study took into account changes in RRT modality during follow-up.

7.2.2.3.5 Period of start of RRT with CVD incidence

This study did not find an association between periods of start of RRT with one- and five-year CVD incidence. There was limited power to detect differences as the numbers of one- and five-year CVD incident events were small, as reflected in the wide 95% CIs around the estimates. In contrast, the USRDS study that included 1,064 fatal CVD events reported that patients who started RRT in later time periods had a lower risk of CV mortality compared to patients who started RRT in earlier periods (120). The larger number of events provided much greater statistical power compared to the current study. Better awareness of high risk of CVD in this population and better management of CVRFs might have resulted in improved CVD-free survival.

7.2.3 Limitations of the study

7.2.3.1 Limitations resulting from data linkage

As data on causes of death and hospital admissions required to identify outcomes are only available in Scotland from 1981 the study was limited to patients who started RRT from 1981 to 2013. The aim of the study was to look at new onset CVD, therefore, patients with prevalent CVD were excluded from the analysis of CVD incidence in the main analysis. However, it is possible that some CVD events occurred among the study

population prior to 1981. It would have been ideal to have access to full records for everyone from birth in order to identify all CVD events prior to RRT. The sensitivity analysis including patients with recurrent CVD showed that patients with a prior history of CVD had a higher risk of CVD compared to patients who were CVD-free at the start of RRT. If patients with recurrent CVD events were included in the analysis of CVD incidence then the incidence and the associations of determinants with CVD might be overestimated. However, it is unlikely that the number of patients for whom prevalent CVD status was misclassified would be large.

7.2.3.2 Limitation of the CVD coding

For the primary analysis using the broad definition of CVD almost all codes for diseases of the circulatory system were used apart from those for hypertension and arteriovenous fistula. Hypertensive disease was excluded from the definition of non-fatal CVD events, as for the purpose of this study it is considered as a risk factor rather than the outcome. However, if a patient died from hypertensive disease it was included in the definition of CVD in order to maximise the power of the study. The arteriovenous fistula procedure codes were excluded from the definition of CVD as this is a standard procedure which is a part of the preparation for HD treatment.

The biggest group of CVD events was “other disease of the circulatory system”, and included heterogeneous types of CVD categories that might represent less severe CVD events. Therefore, these outcomes were not included in the secondary analysis using a stricter definition for CVD. Results of the secondary analysis showed slightly higher HRs suggesting stronger association between determinants with more severe types of CVD events.

7.2.3.3 Bias and confounding factors

Similarly to the ESPN/ERA-EDTA (Chapter 3) and the SRR all-cause mortality analyses (Chapter 5) CV death may be overestimated when obtained from death certificates (156). This overestimation may result in the overall overestimation of CVD incidence, as the definition of CVD incidence included fatal and non-fatal CVD events.

It was not possible to adjust for comorbidities and proteinuria as important confounding factors because these data are not available in the SRR and information on comorbidities was not requested in the linked data.

7.2.3.4 Missing data

Patients with missing data were excluded from the analysis. Excluded patients were older compared to the complete cohort. The explanation of the possible effect it could have on the estimates are presented in previous chapter section 5.4.3.2.

7.2.3.5 Time limitation

Originally I planned to use another renal dataset called Strathclyde Electronic Renal Patient Record (SERPR) in addition to the SRR. The SERPR is a hospital-based renal database, which contains biochemistry, haematology, radiology, pathology, microbiology test results and medication data of patients with all stages of CKD in Scotland. It is a relatively new renal system, which was introduced in adult renal services in Scotland in June 2010 and saw the amalgamation of paediatric data in May 2012. Since the SERPR contains much detailed clinical data on CVRFs than the SRR it was planned to use these data to describe the association of CVRFs (hypertension, obesity, dyslipidaemia and anaemia) with CVD. However, the SERPR data have never

been used for research purpose before and the data manager had to learn new programming skills in her spare time in order to extract the data from the database. This resulted in significant delay in my receiving data for analyses. Therefore, it was decided to restrict my analysis to the SRR data.

7.2.4 Strengths of the study

The main strength of this study is the linkage of the SRR data with the causes of death and CV hospital admissions to be able to describe CVD incidence in patients who initiated RRT in childhood in Scotland. To my knowledge, this is the first study that has described fatal and non-fatal incident CVD events in children who have received RRT in Europe. Furthermore, this study had the longest follow-up period among available studies and included both dialysis and transplanted patients to make a comparison between sub-groups. Most of the available studies used only fatal CVD events, included selected RRT populations and had short follow-up periods.

This is the first study that has explored the associations of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with CVD incidence over a long follow-up period. Only a very small proportion of patients was excluded from the analysis due to missing PRD which is unlikely to have a large influence on these results.

7.2.5 Conclusion and future research

This study highlights the fact that CVD is common among patients who initiated RRT in childhood in Scotland. Cerebrovascular disease is the most common specific type of CVD in this population. Male sex, PRD other than CAKUT or GN and receiving dialysis are significantly associated with a higher risk of developing CVD after initiation of RRT compared to females, patients with CAKUT and patients receiving

a kidney transplantation, respectively. Further research is needed to clarify whether treatment of CVRFs will reduce the risk of CVD in this specific patient population.

However, the small sample size and limited statistical power of the study precluded the potential to draw meaningful conclusions for clinical practice. Future studies are needed with a large sample size to validate these findings. Moreover, studies with data on CVRFs are needed to explore the association of hypertension, obesity, dyslipidaemia and anaemia with CVD incidence in children receiving RRT. A detailed discussion of the scope for future research is discussed in details in the next chapter.

Chapter 8. Discussion

This chapter begins with a summary of the results from the different parts of the thesis: the two literature reviews and the analyses performed in the ESPN/ERA-EDTA and the SRR data. This is followed by the strengths and limitations of the thesis. This chapter also addresses the implications of the findings for clinical practice and future research and proposes recommendations for how the ESPN/ERA-EDTA and SRR can be further enhanced for use in research, followed by an overall conclusion of the thesis.

8.1 Summary of principal findings of the thesis

8.1.1 Findings from the literature review on the prevalence of CVRFs and their association with all-cause mortality and CVD outcomes

The literature review presented in Chapter 2 showed that little knowledge exists about the prevalence and patterns of CVRFs and their association with all-cause and CV mortality in children who receive RRT. In total, 38 studies were included for the literature review of the prevalence of CVRFs. Most of the available studies were performed by single centre studies from the US (65-67, 77, 78, 84-86, 99, 100), Israel (68, 69), Australia (70), Mexico (79), Hungary (80), Austria (70, 87), Turkey (88, 89), Canada (90), Serbia (91), Iran (92), Finland (93) and Sweden (94). Multicentre studies were mostly performed using data from the national and international renal registries (22, 37, 40, 42, 54, 64, 71, 72, 81, 95, 96). The included studies showed that hypertension, anaemia, dyslipidaemia and overweight/obesity are common in patients who initiated RRT in childhood. However, the prevalence estimates of CVRFs varied widely across the studies. No studies described combinations of traditional and uraemia-related CVRFs.

The heterogeneity between studies in terms of their inclusion criteria of the study population and definition of the CVRFs made it difficult to directly compare findings across studies. Several common issues in terms of study quality reporting the prevalence of CVRFs were identified. Potential selection bias and misclassification may have affected the results of the included studies. For example, the majority of the studies were cross-sectional. Therefore, the findings are potentially affected by survival bias. If the patients that were left out of the study were sicker and had a higher prevalence of CVRFs compared to patients who were included in the study, the authors may have underestimated the true prevalence of CVRFs. On the other hand, the authors might have overestimated the true prevalence of CVRFs if prevalence of CVRFs increases with duration of RRT. Additionally, most studies were from single centres with a small sample size that may have resulted in imprecise estimates of the prevalence and may have limited generalisability of their results to wider populations of patients who initiated RRT in childhood within countries or in other countries.

The systematic review of the association of CVRFs with all-cause mortality included limited numbers of studies: three studies for anaemia/Hb (22, 71, 72), two for BMI (54, 107) and two for hypertension (53, 111). Only one study reported on the association between hypertension and cerebrovascular mortality (53). Most studies were based on data collected through national and international renal registries (22, 53, 54, 71, 72, 107), except one single-centre study from Saudi Arabia (111). Results showed that patients with anaemia, hypertension and overweight/obesity have a higher risk of all-cause mortality compared to non-anaemic, non-hypertensive and non-overweight/obese patients, respectively. The only identified study with CV mortality

as the outcome (53) showed that hypertensive patients have a non-significantly higher risk of cerebrovascular mortality compared to non-hypertensive patients.

The quality assessment of the articles included in the systematic review showed that available studies might suffer from selection bias due to exclusion of patients with missing data and the voluntary nature of some registries such as the NAPRTCS and the IPPN. This might have led to underestimation or overestimation of the reported associations between CVRFs and outcomes of interest. However, the characteristics of patients/centres that could not be included in the studies were not provided by the authors, therefore, it was not possible to identify the likely direction of any bias. Furthermore, there might be misclassification of CVRF status among studies that included dialysis populations since patients receiving dialysis experience fluid overload which may have affected the levels of Hb/Ht, BP and body weight (154). This misclassification is likely to be non-differential and bias the reported association towards the null. Despite the limitations the studies included in the systematic review have been performed mostly by the large national and international renal registries that included a large population of patients who initiate RRT in childhood, therefore, offer the best quality data available.

8.1.2 Findings from the literature review of survival and CVD outcomes

My second literature review of survival, CVD outcomes and the association of age at start of RRT, sex, PRD, type of RRT and period of initiation of RRT with all-cause mortality and CVD outcomes (Chapter 4) included 16 observational cohort studies. Most studies used data from national or international renal registries (14, 29-31, 110, 118, 120, 149, 163-169). There was only one single hospital study from Canada (109).

Seven studies showed that patients of young age have a higher risk of all-cause mortality compared to older patients (14, 31, 53, 110, 120, 163, 168). Four studies reported that patients receiving pre-emptive transplantation or a kidney transplant during follow-up period had a lower risk of all-cause mortality compared to patients only receiving dialysis (31, 53, 118, 166). Two studies found a statistically significantly higher risk of all-cause mortality in patients with a PRD other than CAKUT compared to patients with CAKUT (120, 167). Three studies showed that patients who initiated RRT in early years had a statistically significantly higher risk of all-cause mortality compared to patients who initiated RRT in recent years (118, 120, 165).

The majority of the studies reported that CVD was one of the most common causes of death in this population. However, only two studies were found that described incidence of non-fatal CVD events. The USRDS study (164) reported that 31.2% developed a cardiac-related event (mean follow-up not reported) among 1,454 dialysis patients from 0 to 19 years of age. Arrhythmia was the most common type of CVD in this study. Another single centre study from Canada (109) reported that 12.0% of 418 transplanted patients developed CVD during a mean follow-up period of 6.4 years (SD 5.1). Cerebrovascular disease was the most common CVD event. When reviewing the published literature of the association of age at start of RRT, sex, PRD, type of RRT and period of start of RRT with CVD very limited information was found. Only one study explored the association of type of RRT with CVD and the authors did not find a statistically significant association (109).

The major limitations of the available studies are short follow-up period and a low number of events (deaths and CVD incidence) resulting in limited statistical power.

Furthermore, the included studies might suffer from selection bias due to exclusion of patients with missing data from their analyses. Almost all studies had a high proportion of missing data on causes of death. This might have resulted in an underestimation of the CV mortality if there were higher proportion of CV deaths among patients with missing data. However, it is unlikely that a large underestimation occurred as missing data on cause of death is probably likely to be random.

8.1.3 Findings from the ESPN/ERA-EDTA and the SRR analyses

Data on longer-term survival, CVRFs and CVD incidence is scarce in patients with childhood-onset RRT in part because ESRD is rare in children and young adults. This results in low incidence of RRT which leads to small sample sizes and consequently low number of events (death and CVD events) compared to studies performed in adult patients receiving RRT. Moreover, access to morbidity data is necessary to study non-fatal CVD events, which might have been difficult to gain for previous studies. This makes it challenging to perform studies in these populations. In the sections below the findings, limitations and strengths of the ESPN/ERA-EDTA and SRR analyses are summarised.

8.1.3.1 Findings from the ESPN/ERA-EDTA analyses

The analyses of the ESPN/ERA-EDTA registry data covering 33 European countries (Chapter 3) found that hypertension, anaemia, dyslipidaemia and overweight/obesity are common among European patients who initiated RRT from 0 to 20 years old. My findings confirm significant differences in prevalence of the CVRFs by type of RRT. The prevalence of hypertension, dyslipidaemia and anaemia was higher among dialysis patients compared to transplanted patients, while overweight/obesity was

more common among transplanted patients compared to patients receiving dialysis. The most frequent combination of CVRFs among dialysis patients was dyslipidemia, hypertension and anaemia. The combination of dyslipidemia, hypertension and overweight/obesity was most common among transplanted patients.

In the analyses of the association of CVRFs with all-cause and CV mortality I found that anaemic patients had a statistically significantly higher risk of all-cause and CV mortality compared to non-anaemic patients. Underweight patients had a statistically significantly higher risk of all-cause mortality compared to non-underweight patients. I did not find a statistically significant association between dyslipidaemia, hypertension or overweight/obesity and all-cause mortality. Similarly, I found no associations between hypertension, overweight/obesity and underweight with CV mortality. The strengths and limitations of the ESPN/ERA-EDTA analyses are summarised in section 7.3.

8.1.3.2 Findings from the SRR analyses

The analyses of the SRR dataset (Chapter 5 and 6) showed that almost 80% of children who started RRT in Scotland between 1961 and 2013 were still alive after 20 years of follow-up. Furthermore, incident CVD was common developing in 35.2% of the sub-set of children who initiated RRT between 1981 and 2013 (median follow-up 12.9 years (IQR 5.6-21.5)). The results also suggest that patients with PRD other than CAKUT or GN had a higher risk of all-cause mortality and CVD incidence compared to patients with CAKUT. Receiving dialysis rather than a kidney transplantation was associated with a higher risk of all-cause mortality and CVD incidence. Younger age at start of RRT was significantly associated with a higher risk of all-cause mortality.

Males compared to females had a higher risk of CVD incidence. The strengths and limitations of the SRR analyses are summarised in section 7.3.

8.2 Strengths and limitations of the thesis

This section summarises the main strengths and limitations of the thesis. More detailed and specific discussions of strengths and limitations regarding the literature reviews and analyses have been presented in each previous chapter.

8.2.1 Strengths of the literature reviews

Before conducting the analyses in the ESPN/ERA-EDTA and SRR, specific systematic literature searches including critical appraisal of the identified papers have been performed. The main strength of the systematic review of CVRFs is inclusion of several CVRFs (hypertension, dyslipidaemia, anaemia and abnormal BMI) and several outcomes (all-cause mortality, CV mortality and morbidity). Furthermore, besides the searches in Medline and Embase I have also screened annual reports of the national renal registries published on their websites (17, 19) to ensure that also relevant information from this source is reviewed.

8.2.2 Strengths of the ESPN/ERA-EDTA and the SRR analyses

A common strength for both the ESPN/ERA-EDTA and the SRR analyses is the inclusion of incident RRT patients, avoiding survival bias. In contrast the majority of previous studies included prevalent RRT populations subject to survival bias.

Another strength of the ESPN/ERA-EDTA and the SRR analyses is that the data from both dialysis and transplanted patients were included while previous studies mostly focused on mortality risk of either dialysis or transplantation instead of throughout the

entire RRT trajectory. As the majority of children with ESRD receive a kidney transplant, the dialysis studies are subject to selection bias due to inclusion of patients who may have been identified as unsuitable for kidney transplantation in addition to those awaiting a donor. Since patients who remain on dialysis are generally sicker with comorbidities the estimates of mortality would be higher compared to patients who received a kidney transplant. Furthermore, inclusion of both dialysis and transplanted populations permits investigation of potential differences in CVD and mortality by RRT modality, both at initiation of RRT and during follow-up.

A relatively long follow-up period in the ESPN/ERA-EDTA and the SRR analyses increases the power of the study and, specifically for SRR, facilitates long-term follow-up. In contrast, previous studies in general had relatively short-term follow-up and could be subject to survival bias as most deaths occur in the first year after start of RRT with the majority of deaths occurring among children less than 2 years old due to delayed kidney transplantation (169). This may result in overestimation of mortality rates.

8.2.3 Limitations of the literature reviews

There were several limitations of the literature reviews related to the search terms, restriction by year of publication, population and language. Due to that I might potentially miss some relevant papers. First, I did not develop a search strategy specifically to identify papers reporting the prevalence of CVRFs (see Chapter 2 section 2.2.1 for a detailed description). However, I expect that the most relevant data about the prevalence of CVRFs has been included and reviewed because I identified

studies performed by large national and international renal registries reporting this information.

Another limitation of the search strategy for the systematic review is that I did not include narrower search terms for cardiovascular and cerebrovascular disease, for example, coronary heart disease, ischaemic heart disease, stroke, myocardial infarction or ischaemia. However, the medical Subject Headings (MeSH) term “Cardiovascular Diseases” was exploded in the search. This has the effect of including all of the narrower MeSH in the hierarchy, which is a very sensitive and inclusive approach to retrieving records in this broad area of topics. For the complete list of terms included within the exploded heading, see Appendix 3. Relying on MeSH for these areas does depend on the database indexers correctly applying the relevant MeSH, and it is recognised that there is human error or inconsistency in the application of MeSH. This scope for error or inconsistency could have been mitigated against in my search by the use of free-text searches for all of the specific CVD outcomes. This would have been a time-consuming process. Furthermore, as CVD is rare in paediatric RRT population it is unlikely that studies will have sufficient number of patients with specific CVD events to be included in the study and to obtain clinically meaningful results.

In my search I used .mp. rather than .tw. which is more sensitive and in Medline looks for a word or phrase in the title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word and unique identifier. "Textword" (.tw.) searching looks for a word or phrase in the titles or abstracts of the articles only.

For the second literature review focusing on survival/mortality and CVD incidence (Chapter 4) the search only focused on papers published in the last five years. It was a pragmatic approach as inclusion of papers published in recent years would reflect the current clinical situation. Older papers would differ by study population and survival compared to recent papers since improvement in transplantation and dialysis techniques resulted in increased survival in recent years.

I have restricted my search strategy to children. However, adult populations were not excluded in the search. Studies potentially about both child and adult populations would have been captured by the search.

I only included papers published in English. I might potentially miss non-English papers. However, most relevant studies in this area are likely to be published in English because the major registries studies are within English speaking countries or European countries where scientific research is usually published in English language journals. In order to estimate the volume of non-English literature that I missed when conducting my systematic review I used Search Fields in Ovid to isolate any records added to Medline since the completion of systematic review (August 2015). In order to do that I used the format YYYYMMDD with truncation to pick up whole months or years – e.g. 201508$ to pick up whole of August. Then I excluded the records added from August 2015 to obtain the same number of papers that I got in July 2015. Then I separated the English language and non-English language results (see search strategy in Appendix 4). Medline yielded 687 non-English papers.

8.2.4 Methodology of the ESPN/ERA-EDTA and the SRR analyses

Repeated measurements

In my analyses of the ESPN/ERA-EDTA data I summarised repeated CVRFs measurements into one summary measure. This method did not allow me to study whether CVRFs may have a different effect on short-term survival than on long-term survival. One of the approaches to study the effect of the length of follow-up is by reporting mortality rates separately for each year of follow-up (188). For example, Snyder et al. assessed effect of BMI as a fixed risk factor at the start of PD on mortality by reporting yearly mortality rates in 41,197 incident adult PD patients. The authors showed that the effect of obesity at the start of PD on mortality increased over time (189). A Cox regression analysis can also be used to study the effect of a risk factor whose value changes over time. Such risk factors are called time-varying risk factors or time-dependent covariates. In a time-dependent analysis, the follow-up time for each patient is divided into different time windows. A separate Cox analysis is carried out for each time window. After that, a weighted average of all the time window specific results is calculated and presented as one RR. Time-dependent Cox regression model takes into account that risk factors may change over time. However, a time dependent Cox regression provides an answer to a different research question compared with a traditional Cox analysis with only fixed baseline risk factors. A traditional Cox analysis also addresses the relatively long-term effects of a risk factor on mortality, while a time-dependent Cox analysis only addresses relatively short-term effects (188).

Missing data

I used a complete case analyses for both the ESPN/ERA-EDTA and the SRR data analyses. Within each analysis I have excluded patients with missing data relevant to the particular analysis. For the ESPN/ERA-EDTA the percentage of missing data differed for each variable. For example, BMI measurements were quite complete (95%) but only 20% of patients had data on lipids. Excluding patients with missing data might have biased the estimates of the prevalence of CVRFs and their association with all-cause and CV mortality (see complete and more specific explanation in the discussion section of Chapter 3).

In the SRR analyses 6% of patients with missing PRD and/or date of initiation of RRT were excluded. This may have resulted in exaggeration of the estimates of mortality rate and the strength of the association of age at start of RRT with all-cause mortality partly because excluded patients were older compared to the complete cohort. Older patients are more likely to receive a kidney transplant, therefore, have better survival. However, the small proportion of patients with missing data in the SRR analyses means that it is unlikely that there was much exaggeration of the estimates.

Alternative method to deal with missing data would be to perform a multiple imputation of missing data (190). A multiple imputation procedure replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. The multiply imputed data sets are then analysed by using standard procedures for complete data and combining the results from these analyses (190). To be able to perform the imputation of missing data the data have to be missing at random. However, in clinical datasets it is most likely that the data is missing not at

random. For example, more complicated patients with comorbidities are more likely to get their BP, BMI, Hb levels to be measured for better monitoring and treatment of CVRFs, while in healthier patients they would not be not measured or measured less frequently. Therefore, it was not possible to perform multiple imputation of missing data in my analyses. For that reason a complete case analysis was performed.

Comorbidities

Another common limitation is potential residual confounding. Both the ESPN/ERA-EDTA registry and the SRR registry do not include information about comorbidities. Extrarenal comorbidity is common in the paediatric RRT population. The UK Renal Registry reported that at the onset of RRT (2009–2013), 19.3% of children had at least one and 9.5% had two or more comorbidities. The most common types were syndromic diagnosis (8%), developmental delay (7%), and congenital abnormality (7%) (168). The IPPN and the NAPRTCS registries reported that comorbidity is an important predictor of mortality especially for patients with cognitive, cardiac and pulmonary abnormalities in addition to renal disease (157, 191).

8.2.5 Specific limitations of the ESPN/ERA-EDTA analyses

CVRF status might be misclassified particularly among dialysis patients due to fluid overload which might have affected Hb, BP and BMI measurements. Furthermore, information about methods of CVRF measurements was lacking in the registry. A more detailed discussion is presented in Chapter 3. This misclassification is likely to be non-differential which might have biased the association of CVRFs with all-cause and CV mortality towards the null.

Although incident patients are included in the ESPN/ERA-EDTA registry, the measurements of CVRFs were taken at different time points from the start of RRT date. If prevalence of CVRFs increases with duration of RRT the strength of the association between CVRFs and mortality may differ between patients whose measurements were taken at the start of RRT compared to those whose measurements were taken after initiation of RRT. Therefore, to account for that I adjusted my analyses for the time period from start of RRT to the date of first CVRF measurement. Finally, this study design could not clarify whether CVRFs are modifiable risk factors for all-cause and CV mortality or whether all or some of them are acting as markers of the severity of the underlying renal disease.

8.2.6 Specific limitations of the SRR analyses

The main limitation of the SRR analyses is the small sample size and consequently low event rates. This is reflected in borderline statistically significant results and wide 95% CIs for the associations of PRD with all-cause mortality (HR 1.58 (95% CI 1.05-2.39)) and CVD incidence (HR 1.72 (95% CI 1.02-2.91)), and for sex with CVD incidence (HR 1.69 (95% CI 1.05-2.74)). The small number of events occurred despite the median follow-up 18.3 years (IQR 8.7-27.0) for all-cause mortality and 12.9 years (IQR 5.6-21.5) for CVD incidence. Low event rates are of course good for the patients, but does introduce limitations for epidemiological studies.

Another limitation of the SRR analyses is that the records of causes of death and hospital admissions are only available in Scotland from 1981 onwards. For this reason, I had to restrict the study sample to patients who initiated RRT between 1981 and 2013. Even though the characteristics of the linked cohort were similar to the total

cohort I expect that improvement in dialysis techniques and better availability of living-related donors after 1990 in Scotland (personal communication with Glasgow paediatric nephrologists) in part would result in lower CVD incidence compared to the period from 1961 to 1981. Furthermore, inclusion of more recent data is valuable as it reflects the current situation in clinical practice.

8.2.7 Generalisability of SRR findings

The findings of the SRR analysis can be extrapolated to paediatric RRT populations of countries with population, healthcare system and level of income similar to Scotland. It would be inappropriate to extrapolate the SRR findings, for example, to the US population because the population and healthcare system of the US is different from Scotland. The population of Scotland is mainly white with a very low proportion of black people, while the proportion of black people in the US is higher compared to Scotland. Previous research in adult RRT populations showed that the incidence of ESRD is significantly higher in black compared to white population. Scotland has a universal healthcare system that provides health care to all citizens of Scotland. In contrast, the USA has health insurance programs called Medicare and Medicaid which do not cover the whole US population. Approximately 16% of the US population is uninsured. People with and without health insurance may differ in terms of socio-economic status and health conditions. The uninsured people are usually people who cannot afford insurance due to financial difficulties and therefore may be sicker compared to people with health insurance.

Furthermore, it is inappropriate to extrapolate the SRR findings to European countries with lower income compared to Scotland, for example, to eastern European countries.

The ESPN/ERA-EDTA registry previously reported that an increase in public health expenditure was associated with a decreased mortality risk (HR per SD increase 0.69, 95% CI 0.52-0.91) (146). Lower quality of health care system in lower income countries results in poorer accessibility to RRT compared to higher income countries.

8.3 Implication of the findings of the thesis for clinical practice

Implications of the ESPN/ERA-EDTA findings for clinical practice

In this paragraph the implications of the findings of the thesis for clinical practice are discussed. First, the findings from the ESPN/ERA-EDTA registry have demonstrated a high prevalence of anaemia and its association with increased risk of all-cause and CV mortality. One of the main challenges in using these findings to inform clinical practice is the lack of evidence for the effect of treating anaemia in children receiving RRT to reduce the risk of CVD. The systematic review I presented in Chapter 2 showed that there are no RCTs available showing the effect of achieving higher Hb levels on risk of CVD and mortality in children receiving RRT. In the absence of such evidence current guidelines for children receiving RRT are extrapolated from evidence collected in the adult RRT population. In particular, the evidence from cohorts of adults receiving dialysis show that each 1 g/dL decrease in mean Hb is associated with increased odds of LVH (OR 1.46 (95% CI not reported) and recurrent cardiac failure (RR 1.20 (95% CI not reported) (192). The current K/DOQI guidelines recommend treating children with CKD including those treated with dialysis or after kidney transplantation with ESA in order to achieve target Hb levels of 10-12 g/dl (73).

Another finding from the ESPN/ERA-EDTA analyses was the high prevalence of hypertension, dyslipidaemia and obesity in the young European RRT population. Even though this study did not find an association between these CVRFs with all-cause and CV mortality the high prevalence should not be neglected. It might be that these CVRFs have their effect on all-cause and CV mortality after longer-term follow-up into adulthood. This was not possible to describe within the ESPN/ERA-EDTA study because patients were censored when they reach 20 years of age. Previous research in Dutch patients who started RRT in childhood and survived into adulthood showed that hypertensive patients had a higher risk of all-cause and cerebrovascular mortality compared to non-hypertensive patients (53).

No RCTs have been performed in children receiving RRT to demonstrate the efficacy of BP management in preventing CVD. Children with CKD 2-4 in the CKiD study who were treated with angiotensin-converting enzyme (ACE) inhibitor therapy had better control of BP compared to patients who did not receive these classes of agents (193). Research in general paediatric population showed that ACE inhibitor therapy resulted in reduction of LVH (194). Based on these data K/DOQI recommends ACE inhibitors as a preferred antihypertensive agents in children with ESRD and target BP should be lower than the 90^{th} percentile for age, sex and height (73).

In terms of treatment of dyslipidaemia, there is no evidence in the literature of the influence of statin treatment on the development of CVD in children with ESRD. A recent meta-analysis showed that in adults with CKD stage 2-4 statin treatment seems to reduce the risk of CVD, but not in dialysis populations (195). This might be explained by the fact that intimal atherosclerosis, which is most likely to be influenced by lipid levels is an important risk factor for CVD in patients with mild to moderate

CKD. Medial calcification becomes an important risk factor for CVD in advanced stages of CKD and is influenced by factors other than lipids levels (196). K/DOQI guideline recommends screening for dyslipidaemia in children with CKD (including those treated with chronic dialysis and kidney transplantation) to introduce dietary recommendation without initiating treatment with statins (197).

The ESPN/ERA-EDTA analyses found that underweight patients have a higher risk of all-cause mortality compared to non-underweight patients. The aetiology of malnutrition in RRT patients is complex and may include many factors. For example, low food intake may result from anorexia, nausea and vomiting due to uraemic toxicity (152, 198). In addition, bacterial contamination of the dialysis liquid is associated with chronic inflammation (199) which in turn is associated with malnutrition and protein-energy wasting (152). Research in adults receiving dialysis showed that improvement in the bacterial quality of the dialysate is associated with improved nutritional status (200). Therefore, these findings imply that adjusting dietary and caloric intake is needed as well as control of inflammatory and infectious complications in order to maintain BMI and normal growth in children receiving RRT. The NAPRTCS registry showed that growth failure in the paediatric RRT population is associated with increased mortality. The authors reported that mortality risk was twice as high in children with a height SDS<2.5 compared with those of normal height (159).

Implications of the SRR findings for clinical practice

The SRR findings show that the incidence of CVD is high among paediatric RRT patients in Scotland. Therefore, efforts should be made to minimize risk factors for CVD in this population. Most of the CVRFs in the general population, including

hypertension, dyslipidemia, obesity and anaemia are also risk factors for CVD in RRT patients. CVD risk reduction strategies should include: lipid management, control of BMI, BP and Hb level in paediatric RRT population.

The SRR analyses showed an increased risk of mortality in patients receiving dialysis compared to patients following kidney transplantation. The beneficial effect of kidney transplantation on the quality of life and survival of patients with ESRD implies that efforts should be made to increase kidney donation so that more patients could be pre-emptively transplanted or receive a kidney transplant following period of dialysis. Policy makers and clinicians should encourage people to donate their kidneys by informing the public about the need for living donors, and the living donation process. Having accurate and detailed information makes a person more likely to become a donor when they hear that a friend or family member requires a kidney transplantation. Efforts also should be made to increase the number of deceased donor kidneys by encouraging people to register as donors.

The SRR findings also showed that despite the beneficial effect of kidney transplantation mortality rate is still higher among transplanted patients compared to the general population. To improve patient and graft survival among transplanted patients it is important to monitor graft function regularly by performing screening for eGFR level. Detecting kidney allograft dysfunction as soon as possible will allow timely diagnosis and treatment that may improve outcomes.

The SRR findings showed that the risk of mortality was the highest among the youngest RRT patients (<2 years old) who are technically challenging to perform dialysis or a kidney transplantation due to small body size. Therefore, it is particularly

important for the youngest patients to manage PRD. Screening for eGFR, proteinuria and microhaematuria may result in early diagnosis and treatment of PRD that may be beneficial. Furthermore, it is important to control for complications of RRT (infection) and comorbidities in order to allow them the best chance of surviving to receive a kidnay transplant. An international collaboration between the IPPN, ESPN/ERA-EDTA and the ANZDATA registries reported a five-year survival of 76% and a transplant probability of 55% among patients <2 years of age. The authors concluded that relatively good medium-term survival may be achieved in patients <2 years of age despite the high presence of comorbidities (73%) (169).

8.4 Future research

The results of this thesis have added novel and important knowledge to the existing literature describing CVRF prevalence, CVD incidence, all-cause and CVD mortality in patients who initiated RRT in childhood, but there is a scope for future research that is discussed in this section.

Ideally, RCTs would be performed to inform evidence based guidelines for treatment. However, conducting placebo controlled RCTs would not be ethical. The unethical issue of placebo controlled RCT are based on the 1964 Declaration of Helsinki of the World Medical Association that the interest of patients must come before the interests of science and society (201). For example, it would be unethical to use a placebo in a trial of anaemia management because treatments for anaemia that are known to be effective to improve quality of life and reduce mortality in adult RRT population already exist (202). Instead, future trials could potentially test the effect of different doses of ESA on CVD as well as on Hb. Intermediate outcomes such as LVH rather

than hard CVD outcomes would be more feasible for conducting RCTs. The main advantage of RCTs over nonexperimental studies is their ability to control confounding by indication (203). Confounding by indication is a bias that occurs from the differences in prognosis between patients given different therapies in normal clinical practice. It is likely that higher ESA doses will be offered to patients with more severe anaemia. Even if the higher ESA doses are highly effective, the mortality rate among those who receive it could be greater than that among those receiving lower ESA doses, because those who get the higher dose are at the highest risk. This problem can be controlled by the random assignment that is possible in a RCT (203).

Despite the strengths of RCTs there are some important limitations. As ESRD is rare in children it would be challenging to recruit a sufficiently large sample size to provide meaningful results. Furthermore, paediatric patients receiving RRT are heterogeneous in terms of underlying PRD. It will be extremely difficult to include a sufficient number of patients with particular PRD diagnoses due to very low number of patients within specific PRD. In addition, RCTs are often limited to selected populations of patients from unrepresentative centres of care. Multi-centre trials with long follow-up periods are required for adequate numbers of outcomes which will be very expensive.

Taking into account the limitations of RCTs, the most feasible study design in this population of patients at present is to perform retrospective cohort studies using routinely collected data from national and international renal registries linked to hospital admission and mortality records where this is feasible. The benefit of using registry data is that in most cases there is national coverage and these studies are usually less expensive compared to RCTs. This will lead to quicker results because there is no need to wait until CVD occurs. Furthermore, registry studies might be able

to provide long follow-up if the registry has existed for a long time. However, this can also mean that the data collected in earlier years are not always representative for current clinical practice due to change of treatment during follow-up period. Thus, I recommend that retrospective cohort studies using national or sub-sets of international registry data that can be linked to morbidity and mortality data are used to validate and extend the findings of this thesis. In addition, more and better quality data are needed in order to improve the quality of future studies (recommendations for that are described in section 7.6). However, realistically, this study design is also challenging to perform. Even one of the largest renal registries such as the ESPN/ERA-EDTA not able to fulfil the requirements for this study design as it lacks the access to morbidity data for all participating countries. It might be possible to undertake a study in the sub-group of European renal registries that are able to link registry and routine hospital and death record data. Methods for analysing such data without needing data to leave the country of origin are increasingly being used to avoid the problems of international data sharing (204). The USRDS registry might be a potentially good source for future research as this registry has access to morbidity data. I identified one study from this registry that described incidence of cardiac related events in dialysis patients younger than 20 years old (164).

Reverse causality

The ESPN/ERA-EDTA findings of the association of anaemia with CV mortality might be due to reverse causality. Reverse causality refers to a causal relationship that is opposite to what is apparent, e.g., while the observed causal relationship is that F causes Y, the true, actual relationship is that Y causes F (62). It is possible that anaemia is a risk factor for CV mortality in patients with ESRD. However, it is also possible

that CVD causes anaemia. In my analysis of the ESPN/ERA-EDTA data I partly addressed this issue of reverse causality by performing a sensitivity analysis excluding CVRFs measurements taken in the last six months before death. The results of sensitivity analysis were similar to the main results, which means that the association is not entirely explained by reverse causality. In order to investigate weather anaemia is a true risk factor for CVD future prospective cohort studies should include general paediatric populations who are free from CVD and anaemia at the time of the study and follow them up until occurrence of CVD with regular screening for Hb levels. This would allow to explore whether anaemia preceded CVD or CVD caused anaemia.

Another question that remained unanswered within this thesis and could be addressed by future studies is whether hypertension, dyslipidaemia and obesity play a role in risk of CVD in later life after patients who receive RRT as children reach adulthood. The ESPN/ERA-EDTA registry is planning to link paediatric and adult parts of the registry which will enable to investigate the longer-term effects of hypertension, obesity and dyslipidaemia.

There is also scope for future research about paediatric patients receiving RRT in lower-income countries. The studies that I identified in the literature reviews are from middle-income and high-income countries as well as included in my analyses of the ESPN/ERA-EDTA and the SRR. This means that the information that is currently available about children receiving RRT could be biased towards underestimation of mortality due to inclusion of wealthier countries. A few studies available in lower-income countries, where renal registries are often lacking, confirm these disparities. In two tertiary hospitals in Vietnam between 2001 and 2005, only 27% of admitted paediatric ESRD patients received RRT. The remainder were treated conservatively

due to a lack of financial resources (205). In a tertiary hospital in South-West Nigeria the median survival time of 51 admitted paediatric ESRD patients was only 47 days between 2005 and 2012. Of these, 82% had received an acute session of dialysis. However, chronic RRT could not be carried out after discharge due to financial constraints, often resulting in death within months after diagnosis of ESRD (206). In a tertiary care hospital in India, 21% of admitted paediatric ESRD patients were treated conservatively and 40% opted against further treatment due to the high cost of RRT, resulting in death (207). In addition, differences in a country's ability to accept and successfully treat children may be one of the main reasons of disparities in incidence of RRT. Lower-income countries have a lower incidence of RRT compared to middle- and higher-income countries as non-acceptance to RRT results in an underestimation of the incidence of RRT. To illustrate, the incidence of RRT in Nigeria for the years 2009-2012 among children aged≤14 years was 4.4 per MARP (206), while in Europe the incidence of RRT in patients aged 0-14 years was 6.5 per MARP in 2007 (26). Furthermore, country differences in transplant rates, donor source, and time on the transplant waiting list may also affect patient survival indirectly. To conclude, data from middle- and lower-income countries remain scarce. Collecting global data for the paediatric RRT population is essential to determine international disparities in access to RRT and mortality rates and provide evidence for policy change for countries of different levels of income.

8.5 Recommendations for the ESPN/ERA-EDTA and the SRR registries

In this section recommendations for enhancing the data collected within the ESPN/ERA-EDTA and the SRR are discussed. To date, both registries provide the best quality of data available on patients receiving RRT for ESRD in Scotland and in

Europe. However, during the data analyses process I have encountered some limitations within both registries that could be addressed to improve the quality of future studies. First, as retrospective cohort studies rely on existing records stored in the registry database, important information may be missing or unavailable resulting in selection bias. Records with missing data had to be excluded from my analyses of the ESPN/ERA-EDTA and the SRR. There were large proportions of missing data on CVRFs within the ESPN/ERA-EDTA registry. Only a small number of patients had CVRFs measured at the start of RRT, which made it impossible to select a sufficient number of incident RRT patients for my analyses. Therefore, the ESPN/ERA-EDTA registry should collect CVRFs data at the start of RRT for all patients. This will allow researchers to select incident RRT patients and minimise incident-prevalent bias in future studies. However, it is still under debate whether start of RRT should be considered as the first day of RRT initiation. Some studies in adult RRT populations recommend to measure CVRFs at three months after start of RRT. It is because during the first three month after start of RRT the body is adjusting for new therapy, therefore, CVRFs may fluctuate a lot. There are no studies in paediatric RRT populations describing the changes of CVRFs over time after start of RRT. Furthermore, there are no studies exploring whether CVRFs measurements taken at the start of RRT or later play a significant role in prediction of mortality and CVD incidence. Therefore, I recommend for the ESPN/ERA-EDTA registry to collect CVRFs data taken at the start of RRT and monthly within the first year after start of RRT to explore these uncertainties. Furthermore, more data on CVRFs are needed. For example, data on serum Ca, serum P and PTH are available for a very limited number of patients registered in the ESPN/ERA-EDTA registry. For that reason, it was not possible to

explore whether abnormal mineral metabolism is significant risk factor for CV mortality in paediatric RRT patients within my thesis. Also, data on lipids, Hb and BP were incomplete with the registry, which might have biased my results. Therefore, the ESPN/ERA-EDTA registry should collect data on Hb, BP, lipids, serum Ca, P and PTH for all patients in the registry to minimise bias in future studies and to be able to explore remaining research questions.

Second, the methods of CVRF measurement in the ESPN/ERA-EDTA is not provided by participating centres. For example, different centres may use different methods of Hb, BP, lipids and BMI measurements which may introduce misclassification bias in the study.

To address the issue regarding the lack of data on methods of CVRFs measurements the registry could either recommend the method of CVRFs measurement that participating centres should use in order to provide their results to the registry. Alternatively a sub-set of samples from each centre could be measured at a central laboratory as well as at the local laboratory in order to calibrate measurements from different laboratories against each other. However, both requirements could be challenging to fulfil for participating centres. The most feasible recommendation would be for the registry to gather information about the methods of measurements so attempts can be made to correct for different methods in future analyses.

One of the ways to improve the data quality is to show paediatric nephrologists, policy makers and funders the importance of the research that is based on the routine data collected by the renal registries. Paediatric nephrologists should be encouraged by disseminating the findings of the research to them. They could be expected to be more

enthusiastic in providing more and better quality data to the registry if they know that the data are going to be used for research that eventually will improve the health of their patients. Policy makers and funders should also be encouraged to promote the collection of more data by informing them that data collection enhancement could provide higher quality information to patients and parents as well as contributing to higher quality evidence on the prevention of CVD in this population.

The findings of my thesis have been disseminated to paediatric nephrologists in Scotland. I have presented the findings of the ESPN/ERA-EDTA analyses of the prevalence of CVRFs at the Scottish Renal Association (SRA) annual meeting in Dundee on the 2nd October 2015 (oral presentation). I presented the SRR findings in the SRA annual meeting in Inverness on the 28th October 2016 and during a multicentre meeting combining paediatric nephrologists from Glasgow, Newcastle and Belfast held in Glasgow on the 31st May 2017 (both oral presentations). Furthermore, I will present the findings of the SRR analyses in an oral presentation at the upcoming annual ESPN/ERA-EDTA congress in Glasgow on the 7th September 2017.

8.6 Conclusion

My analyses of the ESPN/ERA-EDTA data show that the prevalence of anaemia, hypertension, dyslipidaemia and hypertension is high among young European patients receiving RRT. Being anaemic/underweight is associated with increased risk of all-cause/CV mortality. The SRR analyses showed that CVD is common among patients who initiated RRT in childhood. Younger age at start of RRT, male sex, PRD other than CAKUT or GN and receiving dialysis rather than a kidney transplantation are associated with increased risk of all-cause mortality/CVD in patients who initiated

RRT in childhood. These findings highlight the need for further research to clarify whether treatment of CVRFs is associated with reduced risk of CVD and mortality in this population. RRT for ESRD in children is a rare condition and is challenging to study because of the small sample size and low events rate. This means that future studies should use multi-national renal registries data with long follow-up period and with links to morbidity data where possible. Renal registries should attempt to further enhance the quality of their data to minimise bias in future research. Collecting global data on paediatric patients receiving RRT is essential as a first step in addressing international disparities in this population.

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Appendix 1

MEDLINE search strategy (1946 to July Week 2 2015)

1. (chronic kidney or chronic renal or CKD or impaired renal function or end stage renal disease or ESRD or renal replacement therapy or RRT or dialysis or hemodialysis or haemodialysis or peritoneal dialysis or renal transplantation or kidney transplantation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

2. exp renal replacement therapy/ or exp renal dialysis/ or exp kidney transplantation/

3. exp renal insufficiency, chronic/ or exp kidney failure, chronic/

4. 1 or 2 or 3

5. (death or mortality or all- cause mortality or all-cause death or overall mortality or overall death).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

6. (cardiovascular mortality or cardiovascular death or cerebrovascular mortality or cerebrovascular death).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7. exp Mortality/

8. exp Cardiovascular Diseases/ or exp Cerebrovascular Disorders/ or cerebrovascular morbidity.mp. or cardiovascular morbidity.mp.

9. 5 or 6 or 7 or 8

10. (cardiovascular risk factors or risk prediction score or risk prediction model).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

11. exp risk factors/

12. exp hypertension/ or exp hypertension, renal/ or (hypertension or blood pressure).mp .

13. (Obes$ or overweight or BMI or body mass index or underweight).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

14. exp Obesity/ or exp Overweight/ or exp Body Weight/

15. (anemia or anaemia or target hemoglobin or haemoglobin or iron deficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

16. exp Anemia/

17. (dyslipidemia or dyslipidaemia or hyperlipidemia or hyperlipidaemia or dyslipoproteinemia or dyslipoproteinaemia or abnormal lipid profile or hypercholesterolaemia or hypercholesterolemia or cholesterol or triglycerides).mp. [mp=title, abstract, original title, name of substance word, subject heading word,

keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

18. exp dyslipidemias/ or exp hyperlipidemias/

19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. (child* or paediatric or pediatric or teen* or adolescen* or young adult*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

21. exp Child/

22. 20 or 21

23. 4 and 9 and 19 and 22

24. limit 23 to (English language and humans)

Table 1. Prevalence and patterns of multiple CVRFs in patients receiving dialysis

N of CVRFs	Dyslipidaemia	Hypertension	Underweight	Overweight/ obese	Anaemia	N (%)
0	no	no	no	no	no	5 (0.9)
1	yes					28 (5.0)
		yes				15 (2.7)
				yes		1 (0.2)
					yes	0
			yes			0
Total						***44 (7.9)***
2	yes	yes				155 (27.8)
		yes			yes	16 (2.9)
	yes				yes	12 (2.2)
	yes			yes		10 (1.8)
		yes		yes		6 (1.1)
	yes		yes			2 (0.4)
				yes	yes	1 (0.2)
Total						***202 (36.3)***
3	yes	yes			yes	156 (28.0)
	yes	yes		yes		61 (11.0)
	yes	yes	yes			13 (2.3)
	yes			yes	yes	7 (1.3)
		yes		yes	yes	3 (0.5)
	yes		yes		yes	1 (0.2)
Total						***241 (43.3)***
4	yes	yes		yes	yes	51 (9.2)
	yes	yes	yes		yes	14 (2.5)
Total						***65 (11.7)***

Table 2. Prevalence and patterns of multiple CVRFs in patients after kidney transplantation

N of CVRFs	Dyslipid aemia	Hypertension	Underweight	Overweight/ obese	Anaemia	N (%)
0	no	no	no	no	no	4 (0.5)
1	yes					63 (8.5)
		yes				61 (8.3)
					yes	2 (0.3)
				yes		2 (0.3)
			yes			1 (0.1)
Total						***129 (17.5)***
2	yes	yes				195 (26.5)
	yes			yes		47 (6.4)
		yes		yes		19 (2.6)
	yes				yes	16 (2.2)
		yes			yes	13 (1.8)
		yes	yes			1 (0.1)
	yes		yes			1 (0.1)
Total						***292 (39.6)***
3	yes	yes		yes		189 (25.6)
	yes	yes			yes	64 (8.7)
	yes			yes	yes	9 (1.2)
		yes		yes	yes	4 (0.5)
	yes	yes	yes			2 (0.3)
Total						***268 (36.4)***
4	yes	yes		yes	yes	
Total						***44 (6.0)***

Figure 1. Adjusted Log minus log plot for the association between hypertension and all-cause mortality

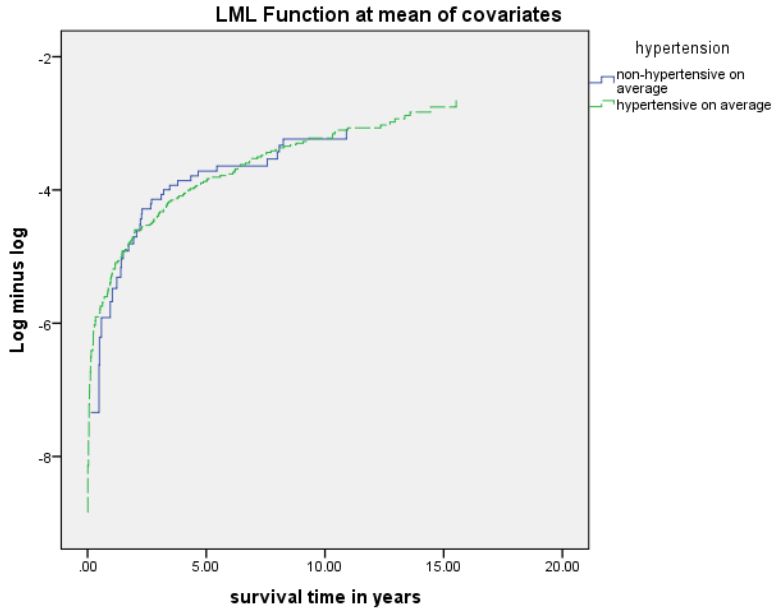


Figure 2. Adjusted Log minus log plot for the association between hypertension and CV mortality

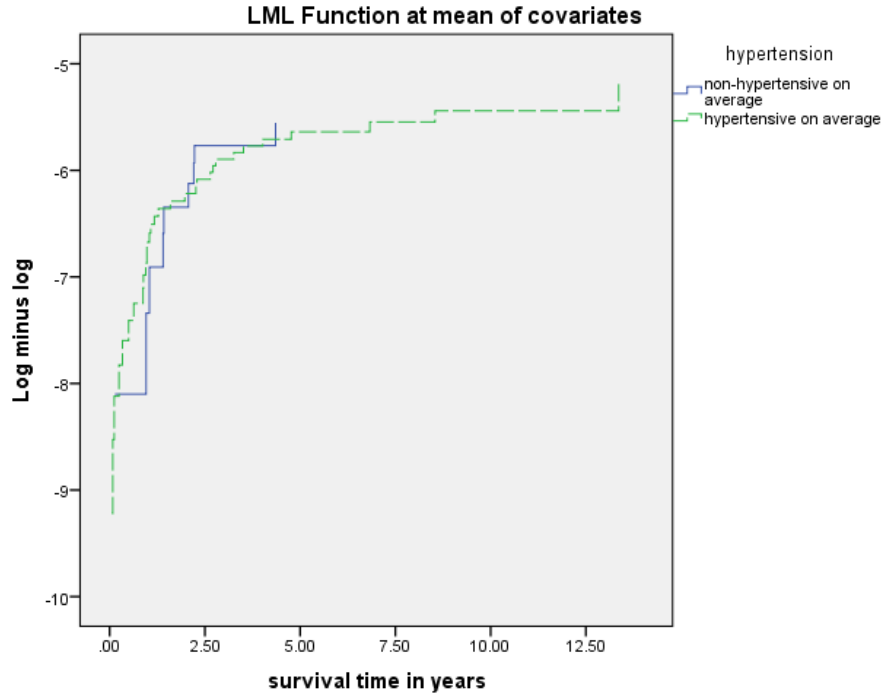


Table 3. Hazard ratios for the association of individual CVRFs with all-cause mortality

CVRFs	N/n	Crude HR and 95% CI	Adjusted* HR and 95% CI
Overweight/Obesity			
Reference group	5222/249	1	1
Overweight/Obese	2224/72	0.62 (0.48-0.81)	1.11 (0.85-1.47)
Underweight			
Reference group	7125/ 273	1	1
Underweight	321/ 48	5.22 (3.84-7.09)	1.81 (1.30-2.53)
Hypertension		*First 2.5 years of follow-up*	
Reference group	1000/ 12	1	1
Hypertensive	3840/ 62	1.29 (0.69-2.39)	1.10 (0.57-2.12)
		2.5 to 6 years of follow-up	
Reference group	1000/ 12	1	
Hypertensive	3840/ 26	0.59 (CI 0.29-1.19)	0.64 (0.30-1.36)
		After 6 years of follow-up	
Reference group	1000/ 7	1	1
Hypertensive	3840/ 43	1.97 (0.84-4.64)	1.82 (0.94-3.52)
Anaemia			
Reference group	3649/ 84	1	1
Anaemic	2049/ 130	3.62 (2.74-4.77)	2.19 (1.64-2.93)
Dyslipidaemia			
Reference group	204/ 2	1	1
Dyslipidaemic	1434/ 41	3.64 (0.87-15.18)	2.09 (0.46-9.44)

N-number of patients, n-number of deaths, HR-hazard ratio, CI-confidence interval. *Adjusted for age, sex, PRD, type and duration of RRT and European region, associations of hypertension with all-cause and dyslipidaemia with all-cause mortality were additionally adjusted for overweight/obesity. Reference group is the group of patients without the CV risk factor

Table 4. Hazard ratios for the association of individual CVRFs with CV mortality

CVRFs	N/n	Crude HR and 95% CI	Adjusted* HR and 95% CI
Overweight/Obesity			
Reference group	5222/57	1	1
Overweight/Obese	2224/17	0.66 (0.39-1.12)	1.44 (0.81-2.55)
Underweight			
Reference group	7125/ 61	1	1
Underweight	321/ 13	5.39 (2.97-9.79)	1.85 (0.97- 3.52)
Hypertension		*First 2.5 years of follow-up*	
Reference group	1000/ 2	1	1
Hypertensive	3840/ 12	1.57 (0.35-7.04)	1.89 (0.40-8.90)
		After 2.5 years of follow-up	
Reference group	1000/ 7	1	
Hypertensive	3840/ 18	0.71 (0.29-1.70)	0.69 (0.28-1.75)
Anaemia			
Reference group	3649/ 13	1	1
Anaemic	2049/ 26	4.37 (2.25- 8.49)	2.55 (1.27-5.12)

N-number of patients, n-number of deaths, HR-hazard ratio, CI-confidence interval. *Adjusted for age, sex, PRD, type and duration of RRT and European region, associations of hypertension with CV mortality was additionally adjusted for overweight/obesity. Reference group is the group of patients without the CV risk factor

Table 5. Prevalence of CVRFs for patients included in primary analyses compared with patients included in sensitivity analyses

CVRFs	Cohort primary analyses	Cohort sensitivity analysis
Dyslipidaemia	87.5	87.6
Hypertension	79.3	79.3
Anaemia	36.0	35.8
Overweight/obesity	29.9	29.9
Underweight	4.3	4.2

Table 6. Hazard ratios for the independent association of CVRFs with all-cause mortality for patients included in primary analyses compared with patients included in sensitivity analyses

		Cohort primary analysis			Cohort sensitivity analysis	
CVRFs	**N/n**	**Unadjusted HR and 95% CI**	**Adjusted HR and 95% CI**	**N/n**	**Unadjusted HR and 95% CI**	**Adjusted HR and 95% CI**
Non Overweight/Obese	5222/249	1	1	5163/190	1	1
Overweight/Obese	2224/72	0.62 (0.48-0.81), p=0.001	1.11 (0.85-1.47), p=0.45	2211/59	0.68 (0.50-0.91) P=0.009	1.16 (0.85-1.58) p=0.46
Non Underweight	7125/ 273	1	1	7064/212	1	1
Underweight	321/ 48	5.22 (3.84-7.09), p<0.0005	1.81 (1.30-2.53), p<0.0005	310/37	5.22 (3.84-7.09) p<0.0005	2.06 (1.39-3.04) p<0.0005
Hypertension		*First 2.5 years of follow-up*				
Non Hypertensive	1000/ 12	1	1	998/10	1	1
Hypertensive	3840/ 62	1.29 (0.69-2.39), p=0.43	1.10 (0.57-2.12), p=0.47	3821/39	1.13 (0.54-2.34) p=0.74	1.03 (0.47-2.22) p=0.45
		2.5 till 6 years of follow-up				
Non Hypertensive	1000/ 12	1	1	998/11	1	1

Hypertensive	3840/ 26	0.59 (0.29-1.19), p=0.09	0.64 (0.30-1.36), p=0.25	3821/23	0.64 (0.31-1.35) p=0.24	0.69 (0.32-1.49) p=0.15
		After 6 years of follow-up				
Non Hypertensive	1000/ 7	1	1	998/6	1	1
Hypertensive	3840/ 43	1.97 (0.84-4.64), p=0.12	1.82 (0.94-3.52), p=0.34	3821/40	2.24 (0.88-5.69) p=0.09	1.71 (0.65-4.49) p=0.27
Non Anaemic	3649/ 84	1	1	3633/68	1	1
Anaemic	2049/ 130	3.62 (2.74- 4.77), p<0.0005	2.19 (1.64-2.93), p<0.0005	2018/99	3.85 (2.79-5.29) p<0.0005	2.35 (1.68-3.29) p<0.0005
Non Dyslipidaemic	204/ 2	1	1	203/1	1	1
Dyslipidaemic	1434/ 41	3.64 (0.87-15.18), p=0.08	2.09 (0.46-9.44), p=0.31	1430/37	6.62 (0.90-48.7) p=0.06	4.38 (0.56-34.3) p=0.46

Table 7. Hazard ratios for the independent association of CVRFs with CV mortality for patients included in primary analyses compared with patients included in sensitivity analyses.

		Cohort primary analyses			Cohort sensitivity analysis	
CVRFs	**N/n**	**Unadjusted HR and 95% CI**	**Adjusted HR and 95% CI**	**N/n**	**Unadjusted HR and 95% CI**	**Adjusted HR and 95% CI**
Non Overweight/Obese	5222/57	1	1	5163/44	1	1
Overweight/Obese	2224/17	0.66 (0.39-1.12) p=0.12	1.44 (0.81-2.55) p=0.21	2211/10	0.50 (0.25-1.00) p=0.05	1.05 (0.51-2.17) p=0.18
Non Underweight	7125/ 61	1	1	7064/44	1	1
Underweight	321/ 13	5.39 (2.97-9.79) p<0.0005	1.85 (0.97-3.52) p=0.06	310/10	6.98 (3.51-13.93) p<0.0005	2.04 (0.96-4.31) p=0.06
Hypertension		*First 2.5 years of follow-up*				
Non Hypertensive	1000/ 2	1	1	998/1	1	1
Hypertensive	3840/ 12	1.57 (0.35-7.04) p=0.55	1.89 (0.40-8.90) p=0.42	3821/7	1.84 (0.22-14.95) p=0.57	3.65 (0.39-33.91) p=0.65
		After 2.5 years of follow-up				
Non Hypertensive	1000/ 7	1	1	998/7	1	1

Hypertensive	3840/ 18	0.71 (0.29-1.70) p=0.44	0.69 (0.28-1.75) p=0.44	3821/18	0.71 (0.29-1.70) p=0.44	0.69 (0.27-1.75)	p=0.44
Non Anaemic	3649/ 13	1	1	3633/9	1	1	
Anaemic	2049/ 26	4.37 (2.25-8.49) p<0.0005	2.55 (1.27-5.12) p=0.008	2018/17	4.26 (1.89-9.61) p<0.0005	2.60 (1.11-6.11)	p=0.008

Figure 3. Type of RRT stratified by age

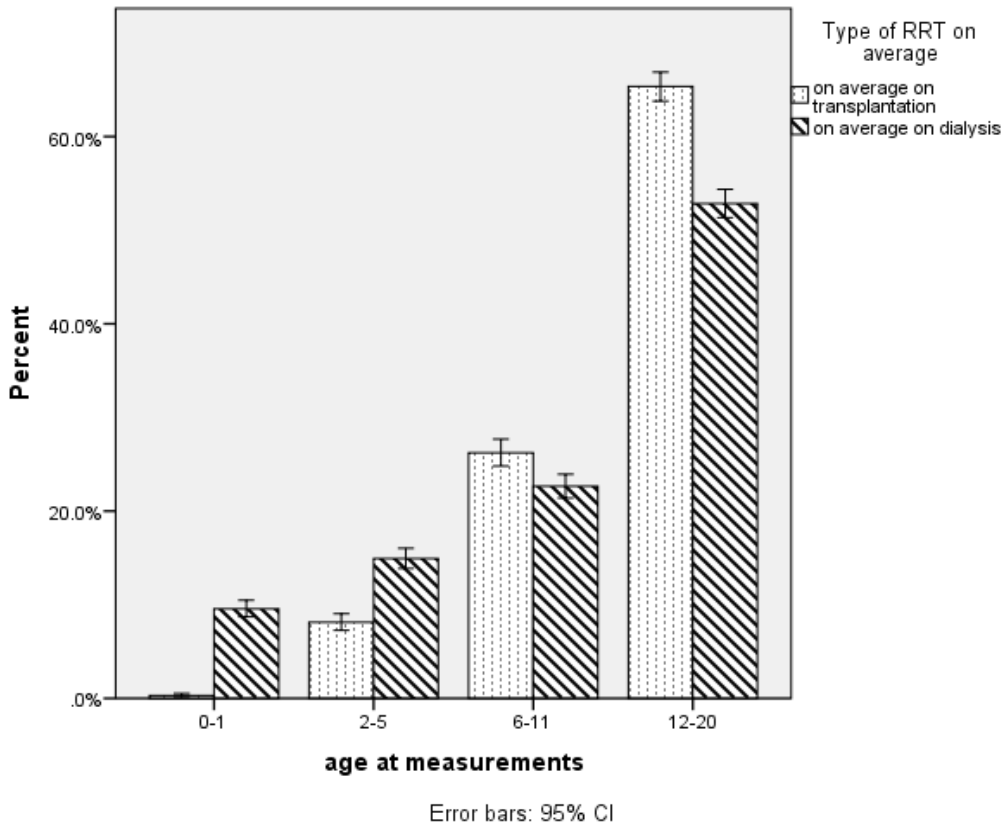


Table 8. Type of RRT stratified by European region

CVRFs	Eastern Europe	Western Europe	Northern Europe	Southern Europe
Dyslipidaemia				
transplanted	18.4	67.7	75.9	27.4
dialysis	81.6	32.3	24.1	72.6
Hypertension				
transplanted	32.5	71.1	79.3	45.4
dialysis	67.5	28.9	20.7	54.6
Anaemia				
transplanted	21.1	53.2	74.4	47.7
dialysis	78.9	46.8	25.6	52.3
BMI				
transplanted	28.5	53.6	72.5	42.0
dialysis	71.5	46.4	27.5	58.0

MEDLINE search strategy

1. (end stage renal disease or ESRD or renal replacement therapy or RRT or dialysis or hemodialysis or haemodialysis or peritoneal dialysis or renal transplantation or kidney transplantation).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

2. exp Kidney Failure, Chronic/ or exp Renal Replacement Therapy/ or exp Kidney Transplantation/ or exp Renal Dialysis/

3. 1 or 2

4. (child* or paediatric or pediatric or teen* or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

5. exp Child/

6. 4 or 5

8. (survival or long-term survival or death or mortality or all- cause mortality or all-cause death or overall mortality or overall death).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

9. exp survival/

10. (cardiovascular disease incidence or cardiovascular disease or cardiovascular death or cardiovascular mortality or cerebrovascular disease or cerebrovascular death or cerebrovascular mortality or cardiac death or cardiac events).mp. [mp=title, abstract,

heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

11. exp cardiovascular disease/

12. 8 or 9 or 10 or 11

13. 3 and 6 and 12

14. limit 13 to human and English and to the last 5 years

Figure 4. Log-log plot for the association of age at start of RRT with all-cause mortality

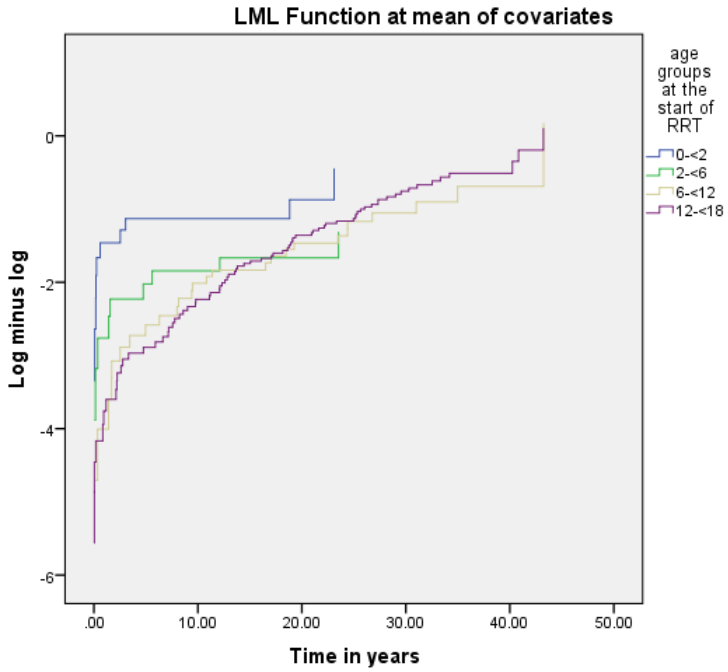


Figure 5. Log-log plot for the association of sex with all-cause mortality

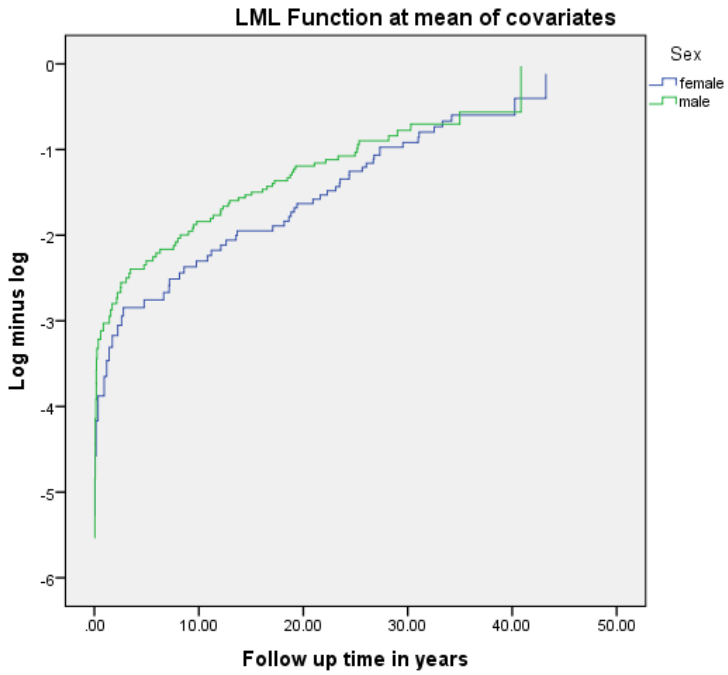


Figure 6. Log-log plot for the association of PRD with all-cause mortality

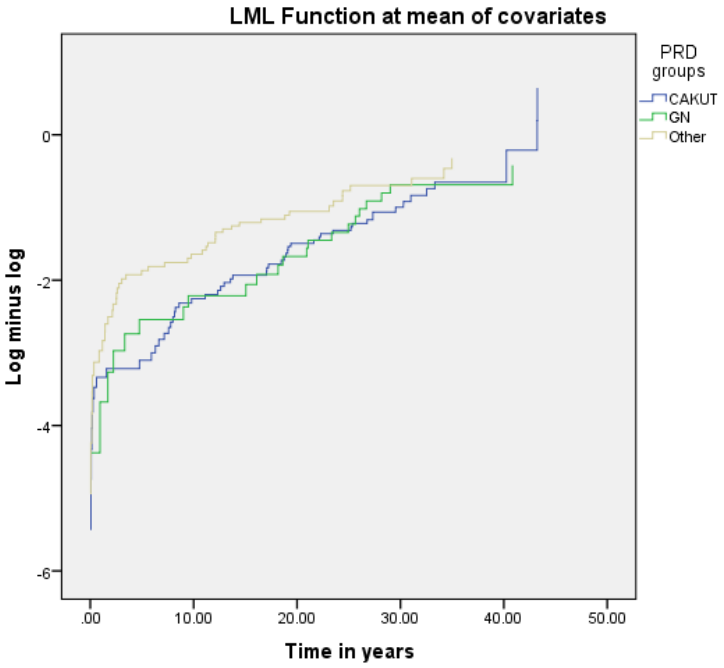


Figure 7. Log-log plot for the association of initial type of RRT with all-cause mortality

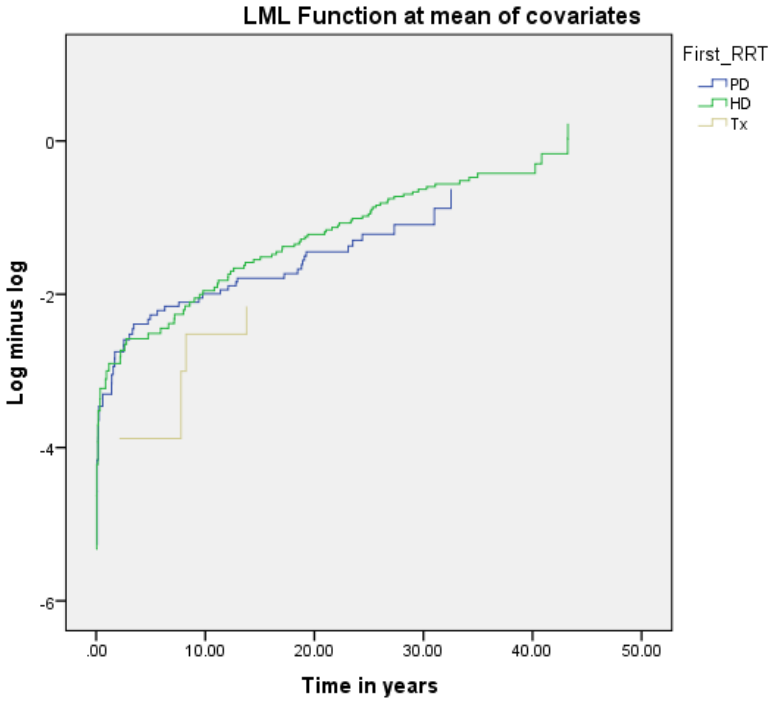


Figure 8. Log-log plot for the association of pattern of RRT modality with all-cause mortality

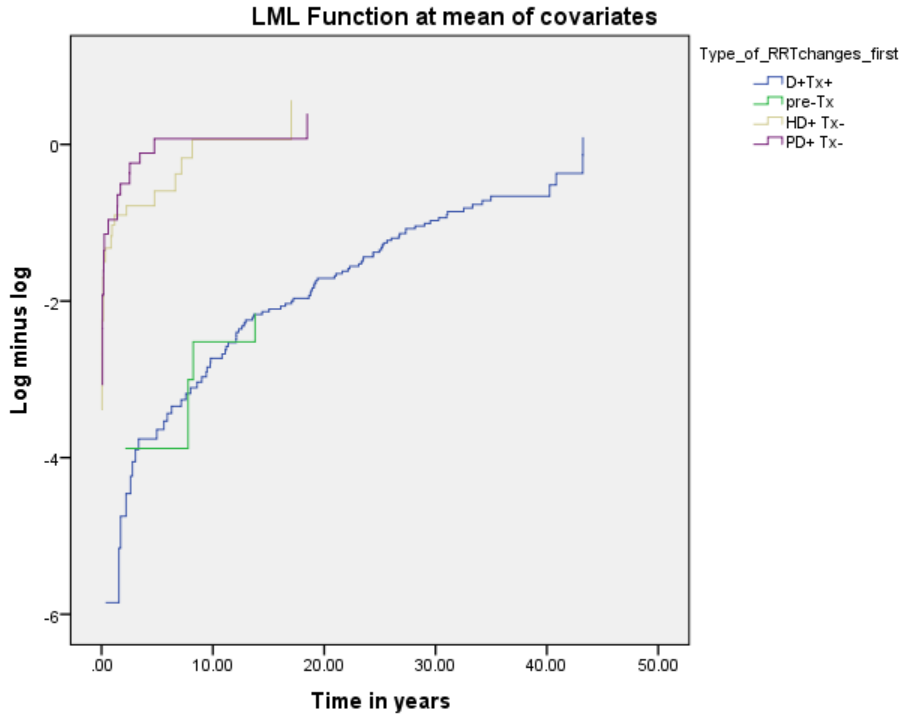


Figure 9. Log-log plot for the association of age at start of RRT with CVD incidence

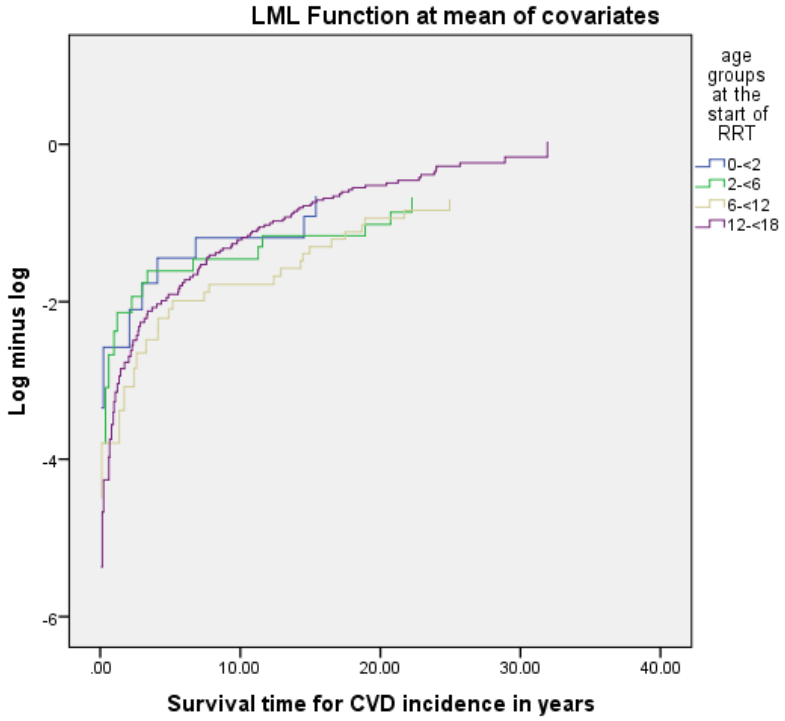


Figure 10. Log-log plot for the association of sex with CVD incidence

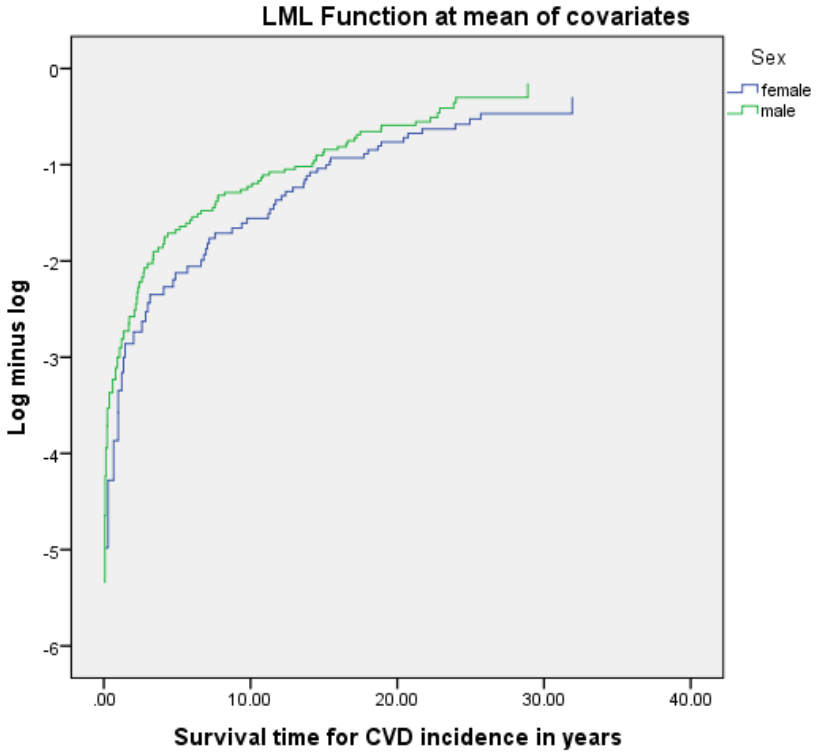


Figure 11. Log-Log plot for the association of PRD and CVD incidence

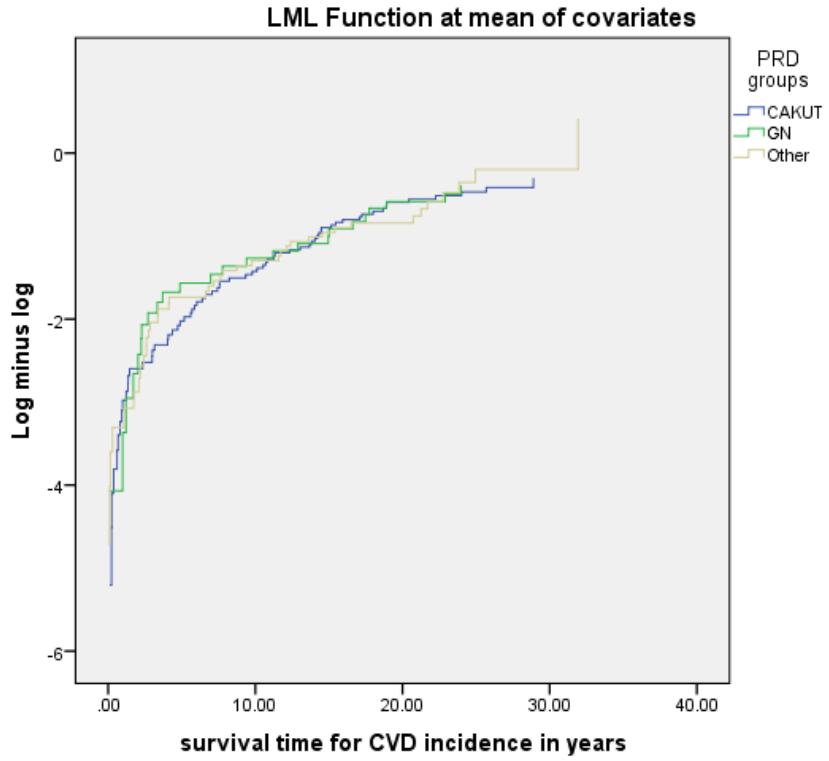


Figure 12. Log-log plot for the association of initial type of RRT with CVD incidence

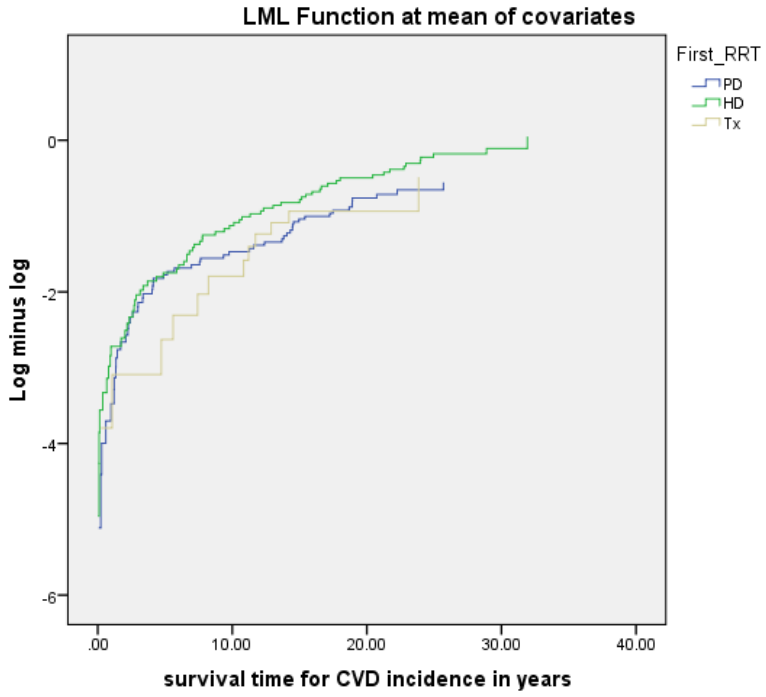


Figure 13. Log-log plot for the association of patterns of RRT modality with CVD incidence

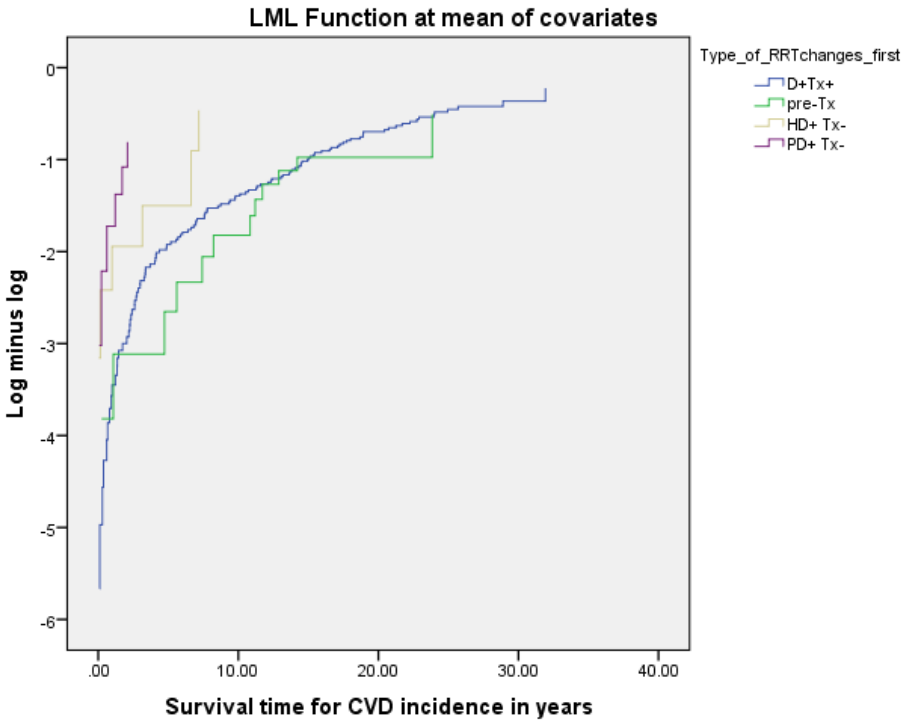


Table 9. Crude and adjusted HRs and 95% CIs of the associations between age at start of RRT, sex, PRD and type of RRT with CVD in the sensitivity analyses

Variable	Primary analysis*		Secondary analysis**	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age at start of RRT[a]				
0-<2	0.90 (0.45-1.79)	1.14 (0.55-2.37)	0.58 (0.21-1.61)	0.77 (0.26-2.25)
2-<6	0.72 (0.42-1.23)	0.92 (0.52-1.65)	0.48 (0.21-1.14)	0.74 (0.29-1.82)
6-<12	0.54 (0.35-0.84)	0.61 (0.38-0.96)	0.66 (0.38-1.16)	0.79 (0.44-1.43)
12-18	1.00	1.00	1.00	1.00
Sex[b]				
Males	1.35 (0.96-1.87)	1.43 (1.01-2.02)	1.23 (0.78-1.95)	1.61 (1.01-2.56)
Females	1.00	1.00	1.00	1.00
PRD[c]				
GN	1.02 (0.65-1.60)	0.96 (0.61-1.53)	1.33 (0.87-2.44	1.23 (0.67-2.29)
Other	1.13 (0.78-1.64)	1.22 (0.83-1.79)	1.45 (0.88-2.36)	1.76 (1.05-2.95)
CAKUT	1.00	1.00	1.00	1.00

Variable	Primary analysis*		Secondary analysis**	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Initial type of RRT[d]				
HD	1.59 (0.87-2.87)	1.19 (0.64-2.22)	2.75 (1.17-6.47)	1.90 (0.79-4.52)
PD	1.15 (0.63-2.08)	1.52 (0.82-2.81)	1.38 (0.57-3.32)	1.56 (0.63-3.88)
Pre-Tx	1.00	1.00	1.00	1.00
Type of RRT during follow-up[e]				
PD+Tx-	2.94 (1.35-6.36)	3.82 (1.61-9.07)	1.77 (0.71-4.41)	5.86 (2.02-17.04)
HD+Tx-	2.19 (1.00-4.79)	2.49 (1.08-5.73)	1.97 (0.94-4.12)	6.68 (2.77-16.12)
Pre-Tx	0.80 (0.45-1.42)	0.82 (0.45-1.47)	0.55 (0.24-1.28)	0.69 (0.29-1.61)
D+Tx+	1.00	1.00	1.00	1.00

PRD-primary renal disease; GN-glomerulonephritis, CAKUT-congenital anomalies of kidney and urinary tract; RRT-renal replacement therapy; HD-haemodialysis; PD-peritoneal dialysis; Pre-Tx-pre-emptively transplanted; HR-hazard ratio, CI-confidence interval. PD+Tx- started on PD and not transplanted during follow up, HD+Tx- started on HD and not transplanted during follow-up, D+Tx+ started on dialysis and received a transplant during follow-up. Only patients with complete data included in unadjusted and adjusted analyses (N=378). *Broad definition, CVD events N=142; ** Strict definition, CVD events N=79; Adjusted for [a] sex, PRD, type of RRT at start and period of start of RRT; [b] PRD, type of RRT at start and period of start of RRT; [c] sex, age at start of RRT, RRT at start and period of start of RRT; [d] sex, age at start of RRT, PRD and period of start of RRT; [e] sex, age at start of RRT, PRD and period of start of RRT

The RECORD statement – checklist of items that should be reported in observational studies using routinely collected health data.

	Item No.	RECORD items	Location in manuscript where items are reported
	1	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Titles of Chapter 5, 6 and 7
Background rationale	2		Chapter 5, section 5.1
Objectives	3		Chapter 5, section 5.1
Study Design	4		Chapter 5, section 5.4
Setting	5		Chapter 5, section 5.2
Participants	6	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process,	Chapter 5, section 5.4

		including the number of individuals with linked data at each stage.	
Variables	7	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Chapter 5, section 5.7, 5.8 and 5.9.2
Data sources/ measurement	8		Chapter 5, section 5.2
Bias	9		
Study size	10		Chapter 5, section 5.4
Quantitative variables	11		
Statistical methods	12		Chapter 5, section 5.9
Data access and cleaning methods		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Chapter 5, section 5.3
Linkage		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Chapter 5, section 5.3
Participants	13	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Chapter 5, section 5.4
Descriptive data	14		Chapter 6, section 6.1.1, Chapter 7, section 7.1.1
Outcome data	15		Chapter 6, section 6.1.6,

			Chapter 7, section 7.1.2
Main results	16		Chapter 6, section 6.1.7, Chapter 7, section 7.1.3
Other analyses	17		Chapter 7, section 7.1.5
Key results	18		Chapter 6, section 6.1, Chapter 7, section 7.1
Limitations	19	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Chapter 6, section 6.2.3, Chapter 7, section 7.2.3
Interpretation	20		Chapter 6, section 6.2.2, Chapter 7, section 7.2.2
Generalisability	21		Chapter 6, section 6.2.4, Chapter 7, section 7.2.4
Funding	22		Chapter 5, section 5.4
Accessibility of protocol, raw data, and programming code		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Chapter 5, section 5.4

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

PRIMA 2009 CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	47
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Not followed
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	47
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	48
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	48
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	50
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	49
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	335
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	50

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	51
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	51
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	52
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not followed
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	52

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	52
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not followed
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	52-55
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	56-66
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	103-106

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	94,97,100
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not followed
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	101-115
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not-followed
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	119-121
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	122
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	123
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not followed

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2

This application should be completed and sent to *NSS.isd-ScotHealthAudits@nhs.net* or
Scottish Healthcare Audits, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB

1. Please select the project you require information on:

- ☐ JAG-Global Rating System (JAG/GRS)
- ☐ Scottish Arthroplasty Project (SAP)
- ☐ Scottish ECT Accreditation Network (SEAN)
- ☐ Scottish Multiple Sclerosis Register (MS)
- ☐ Scottish Stroke Care Audit (SSCA)
- ☐ The Musculoskeletal Audit (MSk)
- ☐ Scottish Audit of Surgical Mortality (SASM)
- ☐ Scottish Intensive Care Society Audit Group (SICSAG)
- +☐ Scottish Renal Registry (SRR)
- ☐ The Scottish Trauma Audit Group (STAG)

2. Details of person requesting data and who will be responsible for them.

Name: Dinara Galiyeva **Designation:** PhD student

Project: The prevalence and patterns of cardiovascular risk factors and their association with all-cause mortality, cardiovascular mortality and cardiovascular morbidity in people who develop end stage renal disease in childhood.

Place of Work: The University of Edinburgh, Usher Institute of Population Health Sciences and Informatics

Postal Address: The University of Edinburgh, Old medical school, Teviot place, Edinburgh **Post code:** EH8 9AG

Tel No: +44 7557850375 **Fax No:-**

Email: Dinara.Galiyeva@ed.ac.uk

3. Details of other staff involved in the project who will have access to confidential data

Name: Professor Sarah Wild **Designation:** Professor of Epidemiology and Honorary Consultant in Public Health, NHS Lothian

Project: The prevalence and patterns of cardiovascular risk factors and their association with all-cause mortality, cardiovascular mortality and cardiovascular morbidity in people who develop end stage renal disease in childhood.

Place of Work: The University of Edinburgh, Usher Institute of Population Health Sciences and Informatics

Postal Address: The University of Edinburgh, Old medical school, Teviot place, Edinburgh **Post code:** EH8 9AG

Tel No: 0131 651 1630 **Fax No**: 0131 650 6868

Email: Sarah.Wild@ed.ac.uk

Please add details of any other colleagues who will be involved on the reverse of this page or below if you are submitting this document electronically.

Name: Dr Nynke Halbesma **Designation:** Research fellow

Project: The prevalence and patterns of cardiovascular risk factors and their association with all-cause mortality, cardiovascular mortality and cardiovascular morbidity in people who develop end stage renal disease in childhood.

Place of Work: The University of Edinburgh, Usher Institute of Population Health Sciences and Informatics
Postal Address: The University of Edinburgh, Old medical school, Teviot place, Edinburgh **Post code:** EH8 9AG

Tel No: 0131 651 7112 **Fax No**: -

Email: Nynke.Halbesma@ed.ac.uk

Name: Dr Caroline Jackson **Designation:** Chancellor's Fellow

Project: The prevalence and patterns of cardiovascular risk factors and their association with all-cause mortality, cardiovascular mortality and cardiovascular morbidity in people who develop end stage renal disease in childhood.

Place of Work: The University of Edinburgh, Usher Institute of Population Health Sciences and Informatics

Postal Address: The University of Edinburgh, No.9 Edinburgh Bioquarter, 9 Little France Road, Edinburgh
Post code: EH16 4AX

Tel No: - **Fax No**: -

Email: Caroline.Jackson@ed.ac.uk

4.
Data Requested:

Please be specific. We will try to provide exactly the information you want but this is sometimes very difficult where a request has not been carefully specified. Where linkage is to be requested, which datasets will be included?

Informal prior discussion with a member of the relevant steering group is usually helpful.

The population of interest is people who developed end-stage renal disease in childhood whose data are stored within Scottish paediatric and adult renal registries. Outcomes of interest are all-cause and cause-specific mortality and incidence of cardiovascular disease derived from the most recent linkage of SRR to death and hospital admission records. Additional data (eg. Lipids fractions measurements, records of antihypertensive medication, ESA and lipid lowering therapy may be required from the paediatric renal register (Strathclyde Electronic Renal Patient Record (SERPR)).

The list of variables requested from renal registries is:

-month and year of birth

-sex
-race

- Scottish Index of Multiple Deprivation or historical postcodes so this can be derived by lookup tables
- Health Board or historical postcodes so this can be derived by lookup tables

-primary renal disease
-eGFR and dates of measurement

-date of start of renal replacement therapy (RRT)

-type of RRT at start

-changes in RRT and dates of measurement all on the same row

- height and dates of measurement for value recorded closest to start of RRT and subsequent annual measurements, in case if the closest to starting RRT measurement will not be available within SRR we would kindly ask to check if SERPR dataset might provide this measurement

- dry body weight and dates of measurement for value recorded closest to start of RRT and subsequent annual measurements, in case if the closest to starting RRT measurement will not be available within SRR we would kindly ask to check if SERPR dataset might provide this measurement

-BMI and dates of measurement for value recorded closest to start of RRT and subsequent annual measurements, in case if the closest to starting RRT measurement will not be available within SRR we would kindly ask to check if SERPR dataset might provide this measurement

-pre- and post-dialysis systolic and diastolic blood pressure and dates of measurement for value recorded closest to start of RRT and subsequent annual measurements, in case if the closest to starting RRT measurement will not be available within SRR we would kindly ask to check if SERPR dataset might provide this measurement

-total cholesterol and dates of measurement for value recorded closest to start of RRT and subsequent annual measurements, in case if the measurements will not be available within SRR we would kindly ask to check if SERPR dataset might provide these measurements

-triglycerides and dates of measurement for value recorded closest to start of RRT and subsequent annual measurements, in case if the measurements will not be available within SRR we would kindly ask to check if SERPR dataset might provide these measurements

-HDL-cholesterol and dates of measurement for value recorded closest to start of RRT and subsequent annual measurements, in case if the measurements will not be available within SRR we would kindly ask to check if SERPR dataset might provide these measurements

-haemoglobin and dates of measurement for value recorded closest to start of RRT and subsequent annual measurements, in case if the closest to starting RRT measurement will not be available within SRR we would kindly ask to check if SERPR dataset might provide this measurement

-ESA use

-antihypertensive medication (types) and date started and stopped, in case if the measurements will not be available within SRR we would kindly ask to check if SERPR dataset might provide these measurements

- Lipid lowering treatment (types) and date started and stopped, in case if the measurements will not be available within SRR we would kindly ask to check if SERPR dataset might provide these measurements

- date of death

-cause of death
- comorbidities at time of death

-end of follow up date/lost to follow up, date of emigration or date of last vital data

5. Time Period of interest:

Up to the end of 2013

6. Frequency of data (monthly, quarterly...etc.):

Single data extract

7. Group of Patients involved:
Requests for data that will or could allow relevant units to be compared, should be specifically highlighted and the reason stated.

Data that could allow the performance of /or outcomes in relevant units to be identified, requires permission as noted below.

Research projects should be conducted under the guidelines agreed by the relevant steering group.

All individuals who developed ESRD in childhood (identified from age<18 years at first renal replacement therapy)

Differences in outcomes by deprivation decile and Health Board will be explored as potential confounding factors but data by unit will not be requested.

8. To whom should the data be sent?

eDRIS research co-ordinator - Sian Nowell siannowell@nhs.net for linkage to paediatric register, mortality and hospital admissions records

(for non-aggregated data please supply an nhs.net address)

9. Preferred date data required by:

Autumn 2015
(Please note: completion dates will be managed around core work by a member of the Steering Group/Clinical Co-ordinator.

10. The Presentation (eg, excel spreadsheet, SPSS, Text document):

SPSS file

11. The purpose for which the data are required:
eg, NHS Board Needs Assessment, local audit, research, manuscript for publication, teaching,..

The data requested will be analysed for research purposes. The results obtained will be described in one of the chapters of Dr Galiyeva's PhD thesis and also presented in publications and conferences in collaboration with Dr David Hughes and SRR colleagues.

12. Description of the methods used to ensure that confidential data are stored and handled with at least the same degree of care and security as that provided by the Audit, and in accordance with the guidelines issued by the Information Services Division of NHS Scotland. Please include details of where the data will be stored (eg, in a locked filing cabinet in Dr X's office) and how access is controlled (eg, key held only by consultant or department secretary …).

The data will be stored in the eDRIS safe haven

13. Proposed presentations or publications using the data:
A separate guideline describes the audit's rules and advice on publication of data and reports.

The results of the data analysis will be presented in my PhD thesis, Scottish Renal Association meetings, ERA-EDTA or ESPN/ERA-EDTA

congress and peer reviewed publications, with review of material by SRR members prior to submission.

14. Funding

a) Please specify any non-NHS funds which will be used.

b) Any funding that will be required by PHI.

Linkage and safe haven costs will be covered by the student's PhD research funds

15. Do you anticipate that this project will need to be submitted to:

a)The steering group (see Information Request Flowchart) Yes

b) A local research ethics committee? No

c) A multi-centre or national research ethics committee? No

d) The Privacy Advisory Committee at PHI? Yes

e) Caldicott Guardians? Yes

f) Any other regulatory body? /No

If you have answered "Yes" to question b to f please describe your plans. It saves time if the submission to these regulatory bodies is developed jointly by the team requesting the data.
Failure to submit an application to a regulatory body at an early stage can result in long delays.

This application is being submitted in parallel to the new Public Benefit and Privacy Panel (that now covers the function of both the Privacy Advisory Committee and Caldicott Guardians)

16. Details of any proposed collaboration with commercial companies to use or analyse these data:

Not applicable

17. Details of any possible conflict of interest that could compromise subsequent publications:

Not applicable

18. Describe the method of destroying confidential data at the end of the project:
Confidential and patient identifiable data must only be retained for the duration of the project. Long term storage of raw data may be required in order to provide the possibility of validating or checking research methods used in publications. In that case paper documents or data files on a non re-writeable medium can be deposited with the PHI office for safe storage. The envelope should state the project name, the name of the main investigator, the date the data were stored, the date in which the data should be destroyed, the medium, the file type and any special instruction required to read it, the purpose of storing the data (eg, audit trail of published data).

Based on eDRIS guidance with appropriate archiving after publication

19. Confirmation from You
I have read, understood and will adhere to the Information Governance checklist.

a) I agree to use the data from the audit only for the purpose described above in section 11. If further proposals for data analysis or data linkage arise I will submit these for consideration.

b) I understand that the research subgroup may:
- **i) In some circumstances be able to release information without seeking further approval.**
- **ii) Need to seek approval from the Steering Group.**
- **iii) Need to seek further approval from the Privacy Advisory Committee of PHI.**

Signed: …Dinara Galiyeva……

Designation: …PhD student……. Date: …25.09.2015……

University of Edinburgh,

Centre for Population Health Sciences

RESEARCH ETHICS SUBGROUP

Self-Audit Checklist for Level 1 Ethical Review for PGR projects

See Intra website for further information:
http://www.cphs.mvm.ed.ac.uk/intra/research/ethicalReview.php

NOTE to student: *Completion of this form should be under the oversight of your supervisor. A good strategy would be to complete a draft as best you can, then discuss with your supervisor before completing a final copy for your supervisor to sign.*

Proposed Project (State research question and topic area, and briefly describe method/ data. Specify also countries in which data will be collected.):

Research question of the project:

What is the prevalence and patterns of cardiovascular risk factors (CVRFs) and what is their association with all-cause and cardiovascular (CV) mortality and CV morbidity in people who develop end stage renal disease (ESRD) in childhood?

Background

CV disease is a major cause of morbidity and mortality in paediatric patients with ESRD and is reported as either the first or second most common cause of death, with the other being infection [1]. CV disease incidence in paediatric ESRD patients is substantially higher compared to the general age-matched population, at least partly because ESRD patients have a higher prevalence of both traditional (hypertension, dyslipidaemia, obesity) and uraemia-related (anaemia) CVRFs [2].

Several studies have reported a high prevalence of hypertension [3] [4], dyslipidaemia [5], obesity [6] and anaemia [8] [9] in children with ESRD. Hypertension and anaemia have also been found to be associated with an increased risk of death in children

receiving renal replacement therapy (RRT) [7] [10]. However, no studies have been published describing the association of dyslipidaemia, obesity or anaemia with CV mortality in this specific patient population. Furthermore, there are no studies which describe the prevalence of combinations of CVRFs and their association with all-cause and CV mortality in children on RRT.

Therefore, the aim of this project is to describe the prevalence of single and combinations of multiple CVRFs and to investigate the association between CVRFs and all-cause and CV mortality and morbidity in people who develop ESRD in childhood.

Methods

A retrospective cohort study based on secondary analysis of pseudonymised individual level data derived from national Scottish paediatric and adult renal registers linked to hospital and mortality records will be performed. The proposal will be reviewed by the Scottish Renal Register steering group and the national Public Benefit and Privacy Panel Prevalence of traditional and uraemia-related CVRFs and their combinations will be described using register data. Kaplan-Meier analysis and Cox proportional hazards regression will be used to investigate the association between CVRFs (and combinations) and all-cause mortality, cardiovascular mortality and cardiovascular morbidity in different groups of patients (for example by primary renal disease), corrected for possible confounders. No information that might allow individuals to be identified will be used in research output.

References

1. Mitsnefes, M.M., Cardiovascular morbidity and mortality in children with chronic kidney disease in North America: Lessons from the USRDS and NAPRTCS databases. Peritoneal Dialysis International, 2005. 25: p. 120-122.

2. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. . National Kidney Foundation. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1).

3. Mitsnefes, M. and D. Stablein, Hypertension in pediatric patients on long-term dialysis: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Am J Kidney Dis, 2005. 45(2): p. 309-15.

4. Kramer, A.M., et al., Demographics of blood pressure and hypertension in children on renal replacement therapy in Europe. Kidney Int, 2011. 80(10): p. 1092-8.

5. Bonthuis, M., et al., Dyslipidaemia in children on renal replacement therapy. Nephrol Dial Transplant, 2014. 29(3): p. 594-603.

6. Bonthuis, M., et al., Underweight, overweight and obesity in paediatric dialysis and renal transplant patients. Nephrol Dial Transplant, 2013. 28 Suppl 4: p. iv195-iv204.

7. Jaap W Groothoff, M.P.G., Martin Offringa, Jeroen Hutten, Marc R Lilien, Nicole J Van De Kar, Eric D Wolff, Jean Claude Davin and Hugo S A Heymans, Mortality and causes of death of end-stage renal disease in children: A Dutch cohort study. Kidney International (2002)61,: p. 621–629;.

8. NAPRTCS 2011 Annual Dialysis Report. 2011.

9. van Stralen, K.J., et al., Prevalence and predictors of the sub-target Hb level in children on dialysis. Nephrol Dial Transplant, 2012. 27(10): p. 3950-7.

10. Warady BA, M.H., Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol, 2003. 18: p. 1055–1062.

1. Bringing the University into disrepute

Is there any aspect of the proposed research which might bring the University into disrepute? NO

2. Data protection and consent

Are there any issues of DATA PROTECTION or CONSENT which are NOT adequately

dealt with via established procedures?

NO

These include well-established sets of undertakings. For example, a 'No' answer is justified *only if*:

(a) There is compliance with the University of Edinburgh's Data Protection procedures (see www.recordsmanagement.ed.ac.uk);

(b) Respondents give consent regarding the collection, storage and, if appropriate, archiving and destruction of data;

(c) Identifying information (eg consent forms) is held separately from data;

(d) There is Caldicott Guardian approval for (or approval will be obtained prior to) obtaining/ analysing NHS patient-data.

(e) There are no other special issues arising about confidentiality/consent.

3. Study participants

Will a study researcher be in direct contact with participants to collect data, whether face-to-face, or by telephone, electronic means or post, or by observation? (eg interviews, focus groups, questionnaires, assessments)

NO

4. Moral issues and Researcher/Institutional Conflicts of Interest

Are there any SPECIAL MORAL ISSUES/CONFLICTS OF INTEREST?

NO

(a) An example of conflict of interest for a researcher would be a financial or non-financial benefit for him/herself or for a relative of friend.

(b) Particular moral issues or concerns could arise, for example where the purposes of research are concealed, where respondents are unable to provide informed consent, or where research findings could impinge negatively/ differentially upon the interests of participants.

(c) Where there is a dual relationship between researcher and participant (eg where research is undertaken by practitioners so that the participant might be unclear as to the distinction between 'care' and research)

5. Protection of research subject confidentiality

Are there any issues of CONFIDENTIALITY which are NOT adequately handled by normal tenets of confidentiality for academic research?

NO

These include well-established sets of undertakings that should be agreed with collaborating and participating individuals/organisations. For example, a 'No' answer is justified *only if*:

(a) There will be no attribution of individual responses;

(b) Individuals (and, where appropriate, organisations) are anonymised in stored data, publications and presentation;

(c) There has been specific agreement with respondents regarding feedback to collaborators and publication.

6. Potential physical or psychological harm, discomfort or stress

(a) Is there a FORSEEABLE POTENTIAL for PSYCHOLOGICAL HARM or STRESS for participants?

NO

(b) Is there a FORSEEABLE POTENTIAL for PHYSICAL HARM or DISCOMFORT for participants?

NO

(c) Is there a FORSEEABLE RISK to the researcher?

NO

Examples of issues/ topics that have the potential to cause psychological harm, discomfort or distress and should lead you to answer 'yes' to this question include, but are not limited to:

relationship breakdown; bullying; bereavement; mental health difficulties; trauma / PTSD; violence or sexual violence; physical, sexual or emotional abuse in either children or adults.

7. Duty to disseminate research findings

Are there issues which will prevent all relevant stakeholders having access to a clear, understandable and accurate summary of the research findings if they wish?*

** If, and only if, you answered 'yes' to 3 above, 'stakeholders' includes participants in the research*

Overall assessment

- If every answer above is a definite NO, the self-audit has been conducted and confirms the ***ABSENCE OF REASONABLY FORESEEABLE ETHICAL RISKS*** – *please tick box*

*This means that regarding this study, as currently self-audited, no further ethical review actions are required within CPHS. However, if in the coming weeks/months there is any change to the research plan envisaged now (and outlined above), the study should be **re-audited** against a Level 1 form, because it may be that the change made negates the absence of ethical risks signed off here.*

+

- If one or more answers are YES, then risks have been identified and prior to commencing any data collection **formal ethical review** is required - either:
  - ~ by NHS REC (NB copy of ethics application and decision letter to be sent to CPHS Ethics); or
  - ~ if not to be formally reviewed by NHS REC, then CPHS level 2/3 ethical review required. *[If either of 5 or 7 are answered 'yes' then almost certainly level 3 is required.]*

Two copies of this form should be taken for inclusion in the final dissertation and the original should be returned to the CPHS Ethics administrator.

Student Name : Dinara Galiyeva

Student Signature

Supervisor Name: Professor Sarah Wild

Supervisor Signature *****

*** NOTE to supervisor:** *The CPHS Ethics Subgroup will not check this form (the light touch Level 1 form means we have insufficient detail to do so). By counter-signing this check-list as truly warranting all 'No' answers,* ***you*** *are taking responsibility, on behalf of CPHS and UoE, that the research proposed truly poses no potential ethical risks. Therefore, if there is any doubt on any issue, it would be a wise precaution to mark it as 'uncertain' and contact the Ethics Subgroup as to whether a level 2 form might be required as well. (See Intra Ethics website – URL at top of form)*

hscic Health & Social Care Information Centre

Certificate of training

This certificate is awarded to:

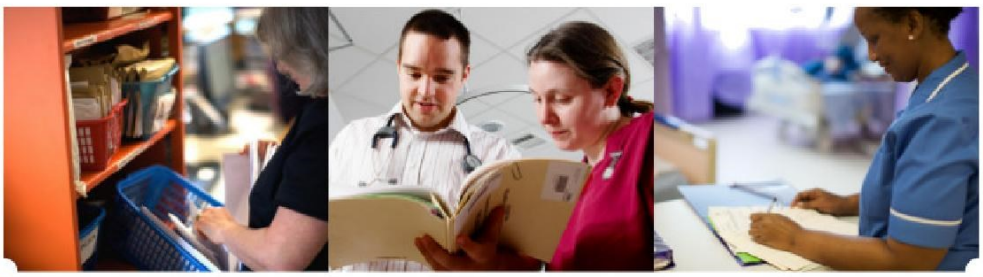
Dinara Galiyeva

for achieving 91% for the e-learning module

Secure Handling of Confidential Information

Introductory level
27 October 2015

Health and Social Care
Information Centre



27 October 2015 15:25:13 - 133 7697

hscic Health & Social Care Information Centre

Certificate of training

This certificate is awarded to:

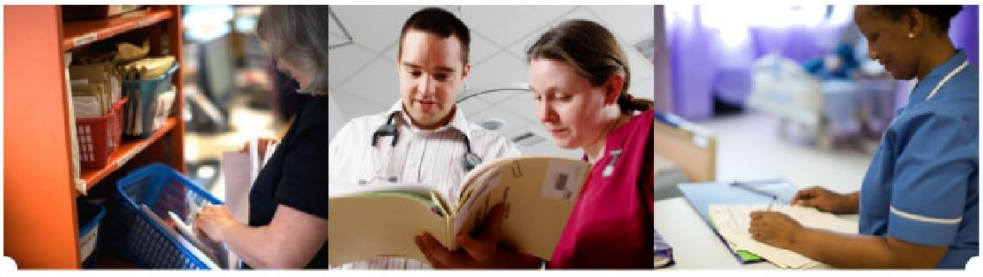
Dinara Galiyeva

for achieving 80% for the e-learning module

The role of the Caldicott/IG Lead in General Practice

Foundation level
23 October 2015

Health and Social Care
Information Centre



23 October 2015 19:02:09 - 1337697

Public Benefit and Privacy Panel for Health and Social Care

Application Form

Application Control *Applicants should not fill out this section*			
Application Coordinator	Sian Nowell		
Application Number	1516-0199	Submitted Date	29.10.2015
Applicant Name	Dinara Galiyeva		
Proposal Name	The prevalence and patterns of cardiovascular risk factors and their association with all-cause mortality, cardiovascular mortality and cardiovascular morbidity in people who develop end stage renal disease in childhood: a retrospective cohort study		

"Amendment to request causes of death and hospital admission data from 1981"

Chronic kidney disease (CKD) in children is a rare but serious condition, as it can progress to end stage renal disease (ESRD), which requires initiation of renal replacement therapy (RRT) in the form of dialysis or kidney transplantation. Mortality rates among children requiring RRT are about 30 times higher than in the age- and gender-matched general population (1), (2). The main cause of death in children receiving RRT is cardiovascular (CV) mortality, which accounts for about 50% of the deaths. Currently we have data on causes of death and hospital admissions from 1997 to 2013, however, due to the fact that CKD in children is rare condition we need the maximum amount of available data on causes of deaths and hospital

admissions starting from the beginning of 1981 until the end of 2013 to improve the power of the current study, specifically in terms of studying CV morbidity (based on hospital admission data) and CV mortality.

References

1. Groothoff JW, Gruppen MP, Offringa M, Hutten J, Lilien MR, Van De Kar NJ, et al. Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. Kidney Int. 2002;61(2):621-9.
2. Stephen P. McDonald aJCC. Long-Term Survival of Children with End-Stage Renal Disease. N Engl J Med. June 24, 2004;350:2654-62.

Contents

Note to Applicants

Prior to completing your application form you should:

- Contact the eDRIS Team, who will assist you - Nss.edris@nhs.net or by phone on 0131 275 7333
- Read and understand the separate Guidance for Applicants

Your application should be typed, not handwritten. Your eDRIS application coordinator will inform you how to submit your application form and any supporting evidence. Before submitting your completed application, you should ensure that:

- All relevant sections of the application are complete
- Relevant supporting evidence is attached
- Individuals named on the form have read and approved its submission

Please note that submitted applications may be circulated to panel members, administrative colleagues, NHSScotland information governance and information security colleagues, Caldicott Guardians, the CHI Advisory Group and, where appropriate, non-NHS Scotland colleagues from a variety of participating partner bodies, in the course

of processing. You must make your eDRIS application coordinator aware of any confidential or sensitive information contained in your application which you would consider inappropriate for circulation in such a manner. Your application could be subject to disclosure or partial disclosure under the Freedom of Information (Scotland) Act, and will be retained in line with NHSScotland information policy.

Section 1 – People

1.1	**Applicant** *Please read section 1.1 of the guidance*	
1.1.01	Full Name:	Dinara Galiyeva
1.1.02	Title:	Miss
1.1.03	Position:	PhD student
1.1.04	Professional Registration No.:	*Not applicable*
1.1.05	Organisation Name:	The University of Edinburgh, Centre for population health sciences
1.1.06	Address:	The University of Edinburgh, Old medical school, Teviot place, Edinburgh
1.1.07	Postcode:	EH8 9AG
1.1.08	Telephone Number:	+44 7557850375
1.1.09	Email:	Dinara.Galiyeva@ed.ac.uk
1.1.10	Do you have an NHS contract/honorary contract?	No
1.1.11	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A, and you should particularly indicate if you have undertaken any of those listed	
	Name of course:	MRC Research Data and Confidentiality online module
	Link to course content:	*http://byglearning.co.uk/mrcrsc-lms/login/index.php*
	Institution:	MRC
	Date completed:	October 2015

1.2	**Clinical Sponsor/Lead** *Please read section 1.2 of the guidance*

1.2.01	Full Name:	Sarah Wild
1.2.02	Title:	Professor
1.2.03	Position:	Professor of Epidemiology and Honorary Consultant in Public Health, NHS Lothian
1.2.04	Professional Registration No.:	GMC 3133196
1.2.05	Organisation Name:	The University of Edinburgh, Centre for population health sciences
1.2.06	Address:	The University of Edinburgh, Old medical school, Teviot place, Edinburgh
1.2.07	Postcode:	EH8 9AG
1.2.08	Telephone Number:	0131 651 1630
1.2.09	Email:	Sarah.Wild@ed.ac.uk
1.2.10	Does this person have an NHS contract/honorary contract?	Yes
1.2.11	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A, and you should particularly indicate if this person has undertaken any of those listed	
	Name of course:	Safe Researcher Training
	Link to course content:	*http://www.adls.ac.uk/safe-researcher-training/*
	Institution:	ADLS
	Date completed:	June 2013

1.3	**Information/Data Custodian** *Please read section 1.3 of the guidance*	
1.3.01	Full Name:	Sarah Wild

1.3.02	Title:	Professor
1.3.03	Position:	Professor of Epidemiology/ Hon consultant in public health
1.3.04	Professional Registration No.:	*3133196*
1.3.05	Organisation Name:	University of Edinburgh
1.3.06	Address:	Teviot Place
1.3.07	Postcode:	EH8 9AG
1.3.08	Telephone Number:	0131 651 1630
1.3.09	Email:	Sarah.wild@ed.ac.uk
1.3.10	Does this person have an NHS contract/honorary contract?	Yes
1.3.11	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A, and you should particularly indicate if this person has undertaken any of those listed	
	Name of course:	Safe Researcher Training
	Link to course content:	*http://www.adls.ac.uk/safe-researcher-training/*
	Institution:	ADLS
	Date completed:	June 2013

1.4 Others with access to identifiable or potentially identifiable data *Please read section 1.4 of the guidance*			
Complete this section if applicable – for each additional person			
Full Name:	Nynke Halbesma	Telephone or Email:	Nynke.Halbesma@ed.ac.uk
Organisation:	University of Edinburgh	Position:	Research fellow

Professional Registration No:		NHS contract/ honorary contract?	No
IG Training - Name of course:	Safe Researcher Training		
IG Training - Link to course:	*http://www.adls.ac.uk/safe-researcher-training/*		
IG Training - Institution:	ADLS	Date completed:	June 2013
Full Name:	Caroline Jackson	Telephone or Email:	Caroline.Jackson@ed.ac.uk
Organisation:	University of Edinburgh	Position:	Chancellor's Fellow
Professional Registration No:		NHS contract/ honorary contract?	No
IG Training - Name of course:	MRC Research Data and Confidentiality online module		
IG Training - Link to course:	*http://byglearning.co.uk/mrcrsc-lms/login/index.php*		
IG Training - Institution:	MRC	Date completed:	July 2015

1.5 Others *Please read section 1.5 of the guidance*			
Complete this section if applicable – for each additional person			
Full Name:		Involvement in Proposal:	
Organisation:		Position:	

Section 2 – Organisations & Bodies

2.1	**Organisation or Body Leading Proposal** *Please read section 2.1 of the guidance*	
2.1.01	Organisation or Body Name:	*University of Edinburgh*
2.1.02	Is this organisation or body a registered data controller? If 'Yes', provide Data Protection Registration Number:	Yes - Z6426984
2.1.03	Is this a commercial organisation or body?	No
2.1.03a	If 'Yes', please provide a full explanation of the organisation or body's activity and industry sector, including any previous experience of using NHSScotland data - append supporting documentation as appropriate	*If applicable*
2.1.04	Is this organisation or body wholly funding or paying for the costs of conducting the proposal?	Yes

2.2	**Organisation or Body Funding Proposal** *Please read section 2.2 of the guidance*	
Complete the following section if you answered 'No' to question 2.1.4		
2.2.01	Organisation or Body Name:	*If the organisation here is an NHSScotland board note this and, go directly to section 2.3*

2.2.02	Is this organisation or body a registered data controller? If 'Yes', provide Data Protection Registration Number:	Choose an item.
2.2.03	Is this organisation or body a commercial organisation?	Choose an item.
2.2.03a	If 'Yes', please provide a full explanation of the organisation or body's activity and industry sector, including any previous experience of using NHSScotland data - append supporting documentation as appropriate	

2.3 Other Relevant Organisations or Bodies *Please read section 2.3 of the guidance*		
Complete this section if applicable		
Organisation Name	Nature of Business/Sector	Nature of interest in proposal

Section 3 – Overview

3.1	**Proposal Essentials** *Please read section 3.1 of the guidance*	
3.1.01	Proposal title/name:	The prevalence and patterns of cardiovascular risk factors and their association with all-cause mortality, cardiovascular mortality and cardiovascular morbidity in people who develop end stage renal disease in childhood: a retrospective cohort study
3.1.02	Is this proposal an extension or renewal of an existing approval (for example to conduct a study over a wider geographic area or for a longer period of time)? Please provide details, include the reference number of the original approval, and summarise the changes requested	No
3.1.03	Is this new proposal related to a previous application (approved or not)? Please give details, indicate if this is a resubmission, including the reference number of the original submission	No
3.1.04	What is(are) the substantive purpose(s) of the proposal? (tick all that apply) ☐ Patient Care ☒ Research ☐ Audit ☐ Performance Monitoring/Management	

	☐ Service Planning/Improvement ☐ Systems Implementation/Testing ☐ Quality (Clinical, Educational, etc) ☐ Health/Social Care Administration ☐ Training/Education	
	If other clearly defined purpose, please give details:	
3.1.05	Does the proposal require the use of information which can identify or potentially identify individuals?	Yes
3.1.06	Access is being requested to data from which sources? (tick as many as are relevant) ☐ A single NHS Scotland Board (excluding NSS) ☒ NHS National Services Scotland ☐ More than one NHS Scotland Board ☒ A national NHS Scotland system/database ☒ More than one NHS Scotland system/database ☐ Community Health Index (CHI) database ☐ NHS Central Registry	
	If other, please give details:	
3.1.07	Provide a full, clear concise outline of the proposal background – describe why it is needed, aims and objectives and envisaged benefits to the public and/or patients: Cardiovascular disease (CVD) accounts for about 50% of the deaths among paediatric patients with end stage renal disease	

	(ESRD) [1], [2]. In contrast, the proportion of deaths due to CVD in the general paediatric population is less than 3% [3]. Risk factors for CVD and mortality were first comprehensively identified in the Framingham cohort study of an adult general population, resulting in the Framingham cardiovascular risk score [4], which includes the traditional cardiovascular risk factors (CVRFs): hypertension, obesity, dyslipidaemia, diabetes and smoking. According to the Kidney Disease Outcome Quality Indicators (K/DOQI) clinical practice guidelines for CVD in dialysis patients these CVRFs are also common among the adult and paediatric ESRD population and contribute to increased risk of CVD [1]. Furthermore, during progression to ESRD different pathological processes specifically caused by abnormal kidney function lead to anaemia, which is also common in the paediatric chronic kidney disease population and may also increase risk of CVD. However, current research conducted in children with ESRD provides very little information about the prevalence of CVRFs and their association with mortality and cardiovascular outcomes. For this reason K/DOQI guidelines for paediatric ESRD population are mostly based on research conducted in adults with ESRD. The prevalence of traditional and uraemia-related CVRFs in children and young adults with ESRD and their association with all-cause, cardiovascular mortality and cardiovascular morbidity is unclear. The main goals of this project are: 1. To describe the prevalence of individual CVRFs, such as hypertension, dyslipidaemia, overweight/obesity and anaemia and combination of them in people who develop ESRD in childhood. 2. To describe the association of above mentioned CVRFs with all-cause mortality, cardiovascular mortality and cardiovascular morbidity in people who develop ESRD in childhood.

The work will be conducted in three stages. The first stage will describe the prevalence of single and multiple CVRFS in children and young adults with ESRD at the start of renal replacement therapy. The second step will describe all-cause and cardiovascular mortality and cardiovascular disease incidence rates for people who developed ESRD in childhood and to compare rates with those for the general population available from http://www.isdscotland.org/Health-Topics/Heart-Disease/Publications/data-tables.asp?id=1475#1475. The final stage is to describe the association between CVRFs and all-cause and cardiovascular mortality and cardiovascular morbidity in people who developed ESRD in childhood.

The results of this work will inform further research, clinical practice and guidelines in paediatric nephrology with the eventual aim of improving outcomes for people who develop ESRD in childhood.

References

1. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. American Journal of Kidney Diseases, 2005. 45.
2. Judith L. Vogelzang, K.J.v.S., Kitty J. Jager and JaapW. Groothoff, Trend from cardiovascular to non-cardiovascular late mortality in patients with renal replacement therapy since childhood. Nephrol Dial Transplant, 2013: p. 2082–2089.
3. Mitsnefes, M.M., Cardiovascular morbidity and mortality in children with chronic kidney disease in North America: Lessons from the USRDS and NAPRTCS databases. Peritoneal Dialysis International, 2005. 25: p. 120-122.
4. Ralph B. D'Agostino, S., Ramachandran S. Vasan, Michael J. Pencina, Philip A. Wolf, Mark and J.M.M.a.W.B.K. Cobain,

	General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study American Heart Association, 2008 117: p. 743-753.
3.1.08	Provide a full, clear and concise outline of the proposal design, listing: data sources; sample size; inclusion/exclusion criteria (eg involvement in trial/survey; health event, etc); relevant date range; need for identifiable or potentially identifiable data; requirement for a matched control cohort etc. **Data sources** The Scottish Renal Register (SRR) and the Strathclyde Electronic Renal Patient Record (SERPR) will be used to identify the cohort of patients who started renal replacement therapy (dialysis or kidney transplant) before they reached 18 years of age and provide risk factor data (hypertension and/or overweight/obesity, and/or dyslipidaemia and/or anaemia). SERPR dataset is needed to provide the data on those risk factors that are not available in SRR, such as lipids measurements, antihypertensive medication and ESA usage. Outcome data to the end of 2013 are available from hospital and mortality records from an existing linkage of SRR data to SMR01/NRS records. **Sample size/ inclusion criteria** Based on all available Scottish data for people developing ESRD in childhood **Time Period of interest:** From start of available data – beginning of 1981 to the end of 2015 Individual level data will be required for analysis but only aggregated data will be presented.

	National age-specific or age-standardised data on all-cause and CVD mortality and CVD incidence will be presented for comparison and a matched cohort will not be required. Reference 1. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. American Journal of Kidney Diseases, 2005. 45.
3.1.09	Does the proposal have implications for, or target, sensitive groups or vulnerable populations? Please give details
	Not from list given below in sections 5 and 6 of appendix 6
3.1.10	Does the proposal seek to use information exclusively about deceased persons? Please give details
	No, not exclusively, but death is one of the outcomes of interest
3.1.11	Have any members of the public/lay representatives been involved in the proposal design? Please give details
	No
3.1.12	Has any peer review of the proposal been undertaken? Please give details (for example formal review by a peer organisation or funding body, informal internal review, review by a third party)
	The main applicant for this proposal is a PhD student of the University of Edinburgh, Usher Institute of Population Health Sciences and Informatics and this project will be one of the main

	chapters of the thesis. This project will therefore be reviewed by the internal ethics committee and PhD review panels within the Usher Institute at the University of Edinburgh. In addition a very similar project describing the prevalence and association of CVRFs and cardiovascular mortality in European children receiving RRT conducted by the applicant was approved as part of a short-term fellowship within the second year of the applicant's PhD by the European Society for Paediatric Nephrology (ESPN) committee. The project was finished on 30.05.2015. The results will be also included in the applicant`s thesis and have been presented at the Annual Scottish Renal association meeting in Dundee in October 2015. The current proposal mainly builds on the ESPN project, but the Scottish data will allow extension of the eligible cohort into adulthood and will also include cardiovascular morbidity as an outcome, which was not possible with the European data.
3.1.13	Is there *any* commercial aspect or dimension to the proposal or its outcomes? Please give details
	no

3.2 Proposal Geography *Please read section 3.2 of the guidance*
☐ Local/Regional (relating to one or more specific areas within Scotland)
☒ National (relating to the whole of Scotland)
☐ UK-wide (relating to the whole of the UK, or to UK regions outside Scotland)
☐ International (relating to areas within the EEA)
☐ International (relating to areas beyond the EEA)

3.3	**Proposal Duration and Frequency** *Please read section 3.3 of the guidance*	
3.3.01	What is the proposed duration of the proposal?	**12 months**
3.3.02	Does the proposal require updates of information at regular intervals? Please give details	**no**
3.3.03	Are you seeking approval to iterate the proposal (ie the *whole* project, audit or study) at regular intervals? Please give details	**no**

3.4	**Statutory and Regulatory Context** *Please read section 3.4 of the guidance*	
3.4.01	Does your proposal have a statutory or regulatory justification - is the proposal responding to a statutory or regulatory instruction, duty or order? Please give details	*No*
3.4.02	Which Data Protection Act schedule 2 and schedule 3 conditions are relevant? (a list of conditions can be found at Appendix B)	Schedule 2, condition 6. Schedule 3, condition 3.
3.4.03	Are there any relevant information sharing agreements, protocols or contracts in place which support your proposal? Please give details and attach as supporting documentation if available	*If applicable*
3.4.04	Has a Privacy Impact Assessment been carried out which supports your proposal? Please give details and	*If applicable*

	attach as supporting documentation if available	
3.4.05	Has local Caldicott approval been given for your proposal at a local level? Please give details	*If applicable*
3.4.06	Are approvals from Caldicott Guardians outside Scotland pending or received? Please give details	*If applicable*

3.5	**Research and Ethics Governance** *Please read section 3.5 of the guidance*	
3.5.01	Has your proposal sought research/ethics approval?	Yes
3.5.01a	If yes, please provide committee details and status of approval (ie pending, approved, etc). Please attach as supporting documentation if available	*Level 1 review of CPHS ethical review, pending (form attached)*
3.5.01b	If no, please explain why research/ethics approval is not sought:	*Not applicable*

3.6	**Safe Havens** *Please read section 3.6 of the guidance*	
3.6.01	Do you intend to access the data requested exclusively through a safe haven listed at Appendix A? Please provide details of which safe haven/s	*Yes* NSS National Safe Haven
3.6.02	If you applying to use NHS NSS data and you do not intend to do this through the National Safe Haven, please explain why	*If applicable*

Section 4 – Data & Data Subjects

4.1 Data yet to be collected *Please read section 4.1 of the guidance*		
Dataset/source Name	Collection by (whom)?	Explicit consent sought? If Yes, describe how explicit consent being sought – provide copies of participant consent/registration forms, etc. If No, explain why consent is not being sought (eg impractical, risk associated with seeking consent, etc)

4.2 All Other Datasets / sources *Please read section 4.2 of the guidance*		
Dataset/source Name	Data Controller (Organisation)	Original purpose compatible with proposal?
Strathclyde Electronic Renal Patient Record (SERPR)	**Susan Burns/ NHS Greater Glasgow & Clyde**	**Yes**
Scottish Renal Registry (SRR)	**ISD**	**Yes**
Mortality records and hospital admissions	**ISD**	**Yes**
How were individuals originally informed of the use of their data? (if known)		
Standard NHS information		

For existing dataset/sources for which the data controller is not an NHSScotland board, please append evidence of the data controllers permission to use the data

4.3 Data Variables *Please read section 4.3 of the guidance*			
Dataset/source Name	Variable	Time Period/Range	Processing only?
Register and SMR01/GRO99	CHI number	For cohort identified from renal register	Yes – for data linkage by eDRIS, to be replaced with a unique identifier in research dataset
SRR	-month and year of birth -sex -race -Scottish Index of Multiple Deprivation -Health Board -primary renal disease -eGFR and dates of measurement -date of start of renal replacement therapy (RRT) -type of RRT at start	Jan 1981 to Dec 2013 The measurement closest recorded to start of RRT and subsequent annual measurements up to the end 2013	No

	-changes in RRT and dates of measurement - height and dates of measurement - dry body weight and dates of measurement -BMI and dates of measurement -pre- and post-dialysis systolic and diastolic blood pressure and dates of measurement -total cholesterol and dates of measurement -triglycerides and dates of measurement -HDL-cholesterol and dates of measurement -haemoglobin and dates of measurement -ESA use and date started and stopped -antihypertensive medication (types)		

	and date started and stopped - Lipid lowering treatment (types) and date started and stopped - comorbidities at time of death -end of follow up date/lost to follow up, date of emigration or date of last vital data - date of death -cause of death		
Death registration	- date of death -all causes of death	Jan 1981 to Dec 2015	No
Hospital admissions records SMR 01	-cardiovascular morbidity outcomes- from hospital admission records (ICD-10 I chapter codes) - date of hospital admissions with cardiovascular disease	Jan 1981 to Dec 2015	
Please justify your need for identifiable or potentially identifiable variables:			

- Age, sex and race are crucial variables in order to make fair comparisons both with mortality in the general population but also for comparison within the cohort, for example for people with different types of kidney disease. As this is a paediatric population month of birth is needed as well as year of birth to improve precision of estimates of age.
To link the data and to control for confounding by age and sex

4.4	**NRS/NHSCR Data Sources** *Please read section 4.4 of the guidance*	
Complete this section if access to NHSCR is required, or if there is any National Records of Scotland involvement		
4.4.01	Does the proposal require access to NHS Central Registry as a sampling frame for cohorts?	No
4.4.02	Does the proposal involve flagging of individuals on the NHSCR for long term follow up?	No
4.4.03	If yes, is flagging necessary: ☐ To trace and contact individuals throughout the UK? ☐ To be informed of fact and cause of death? ☐ To be informed of the incidence of on-going cancers? ☐ To be informed of emigrations prospectively and retrospectively?	
4.4.04	Is any other NRS involvement required? Please provide details	Yes To provide death data

4.5	**Making Contact with Individuals** *Please read section 4.5 of the guidance*

4.5.01	Is any direct contact with any group of individuals required? If Yes, please provide details below				No
	Contact Group and Method of contact				Contact by (whom)
	☐ Hospital Consultants	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ Other NHSS Staff	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ General Practitioners	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ Patients/Public	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ Relatives of participants	☐ Letter	☐ Phone	☐ Other (specify):	
	☐ Others (please specify):	☐ Letter	☐ Phone	☐ Other (specify) :	
4.5.02	Please explain why contact is being made – append copies of relevant correspondence as supporting evidence				
	If applicable				

4.6	**Community Health Index (CHI) Database** *Please read section 4.6 of the guidance*
Complete this section if access to CHI Database is required	

4.6.01	What monitoring and audit of the use of CHI is planned? Please provide details	Not applicable
4.6.02	What technical method will be used to access CHI (online read-only, download, other extract, anonymised extract, etc)? Please provide details	
4.6.03	Have any risks been identified in the proposal which relate specifically to CHI?	

Section 5 – Methodology & Data Processing

5.1	**Methodology** *Please read section 5.1 of the guidance*	
5.1.01	Does the proposal require any of the following: ☒ Data matching/linking ☒ Single anonymised data extract ☐ Use of matched controls Other (please specify):	
5.1.02	Who is carrying out any indexing/ linkage/anonymisation, and where?	*eDRIS*
5.1.03	Which data sources listed at section 4.1 and 4.2 will NSS/NRS receive identifiers for linkage purposes?	*All*
5.1.04	What variables will be provided for linkage? ☒ CHI Number ☐ Forename ☐ Surname ☒ Date of Birth ☐ Address or Postcode ☐ NHS Number Other Please Specify:	

5.2	**Access** *Please read section 5.2 of the guidance*	
Complete the following section if you answered 'No' to question 3.6.1		
5.2.01	At what location is identifiable or potentially identifiable data being accessed?	**Not applicable**
5.2.02	Please provide details of security policy/procedure governing access to this	

	physical and technical environment – append supporting documentation	
5.2.03	Does this policy/procedure cover password policy in detail? Please provide details/ append supporting documentation	
5.2.04	Does this policy/procedure cover user account management, including review or removal of access to sensitive/personal data, in detail? Please provide details/ append supporting documentation	
5.2.05	Will individuals with access to data have individual or shared accounts?	
5.2.06	Will the data be accessed by staff working off site eg staff working from home at any time during the duration of the proposal?	Choose an item.
5.2.06b	If yes, are policies/procedures in place to facilitate, monitor and audit this access? Please provide details/ append supporting documentation	*If applicable*
5.2.07	Provide any additional detail of how data is protected from unauthorised access	*If applicable*

5.3	**Store & Use** *Please read section 5.3 of the guidance*	
Complete the following section if you answered 'No' to question 3.6.1		
5.3.01	Where is data being stored and used? (location, organisation, address – refer to addresses in previous sections if appropriate)	
5.3.02	Data Protection Registration Number	*If applicable*
5.3.03	ISO 27001 Cert. No.	*If applicable*
5.3.04	Please provide details of security policy/procedure governing storage and	

	use of data within this physical and technical environment – append supporting documentation	
5.3.05	Does this policy/procedure cover the implementation of up-to-date controls for the detection and prevention of malware? Please provide details/ append supporting documentation	
5.3.06	Does this policy/procedure cover access control and auditing of system administrator activity? Please provide details/ append supporting documentation	
5.3.07	Does this policy/procedure cover the production of backups and the controls in place around these? Please provide details/ append supporting documentation	
5.3.08	Does this policy/procedure describe the controls in place to prohibit unauthorised copying of data? Please provide details/ append supporting documentation	
5.3.09	Does this policy/procedure describe physical and site controls? Please provide details/ append supporting documentation	
5.3.10	Does this policy/procedure cover hardware repair, replacement or disposal and protection of data from inappropriate access during such procedures? Please provide details/ append supporting documentation	
5.3.11	Describe the systems, software and security used to store and use data -	

	please provide details/ append supporting documentation	
5.3.12	Is outsourced IT in use? Please give details	
Please repeat section 5.3 above for each relevant location in the proposal – see guidance		

5.4	**Transfer** *Please read section 5.4 of the guidance*	
5.4.01	Please provide details of security policy/procedure to ensure that data will be transferred in such a way that it is protected from inappropriate or unauthorised access (mention email encryption, secure file transfer protocols SFTP, device encryption, physical controls, etc, as appropriate) - append supporting documentation	Data will be transferred by secure file transfer
5.4.02	At what intervals/ trigger points will data transfer take place?	At start of study
5.4.03	Will any identifiable or potentially identifiable data be transferred outside of the UK?	No
5.4.03b	If yes, please provide details of the country of destination, the method of transfer, the proposed location and method of storage outside of the UK, and details of any further onward transfer	*If applicable*
5.4.04	Other than initial transfers from source systems, is there any copying of data required within the proposal? Please give details	No

5.5	**Dissemination** *Please read section 5.5 of the guidance*	
5.5.01	Will proposal findings be published or disseminated beyond the proposal team?	Yes *If you have answered 'No', go directly to section 5.6*
5.5.01a	If yes, how will proposal findings be published or disseminated, to what audience and in what format? Please give details	*Abstracts to renal conferences and peer reviewed papers*
5.5.01b	If yes, what steps will be taken to ensure that persons cannot be identified in published findings (eg disclosure control procedures (safe haven), use of aliases, numbers, avoidance of small geographical areas, avoidance of small numbers, etc)? Please give details	*No cells in published work will contain fewer than 5 individuals*
5.5.01c	If yes, are there any circumstances where a living or dead individual would be cited? (eg where a person consented to their data being used as a case study)? Please give details	*No*
5.5.01d	If yes, were any permissions to publish data required or sought (for example from data controllers)? Please provide details	*Not applicable*

5.6	**Retain/Dispose** *Please read section 5.6 of the guidance*	
5.6.01	Which information/data/records retention policy will you be applying to the proposal data (details of the policy and the organisation to which it belongs)?	NSS National Safe Haven safe haven policy

5.6.02	How long do you intend to retain identifiable or potentially identifiable data after the conclusion of the proposal (including archive/backup copies)?	As advised by eDRIS
5.6.03	Who will retain the data and where?	NSS National Safe Haven
5.6.04	What is the purpose for retaining the data for the specified time?	For research governance purposes
5.6.05	What method of disposal or destruction will be used when this period has expired (including archive/backup copies)?	NSS National Safe Haven destruction policy
5.6.06	What evidence will be obtained that destruction has occurred (eg IT supplier certificate of destruction, etc)?	NSS National Safe Haven destruction policy

5.7	**Review** *Please read section 5.7 of the guidance*	
5.7.01	Describe how the mechanisms which safeguard data security will be audited and reviewed at regular intervals to ensure their continued efficacy	Data will only be accessed by the applicants and information custodian via the safe haven
5.7.02	Describe any resource implications to any of the proposed measures for the protection of physical or technical security of information which are unresolved at the time of this application? (for example encryption of devices is an intention not yet fulfilled, training is not yet undertaken, etc)	NA
5.7.03	Describe the breach reporting mechanisms to be invoked in the event of	Any data breach will be immediately

	any inappropriate access to data or other information security incident	reported to the safe haven manager

Section 6 – Declaration

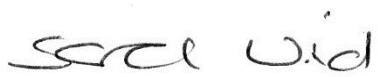
- I DECLARE THAT this application is accurate, and that, should it be successful, any health data made accessible will be used for no other purpose, and in no other way, than as described above.
- I UNDERTAKE TO notify the Public Benefit and Privacy Panel of any future changes to the purpose or manner in which data is processed in accordance with this application.
- I UNDERSTAND THAT any future applications by me, or my employing or sponsoring organisation, may be refused should any health data made accessible be used for any other purpose or in any other way than that described above.
- I CERTIFY THAT all those who have access to health data in this proposal are aware of the requirements of confidentiality and understand that any breach (eg disclosure of confidential information to a person not authorised to receive it) will be reported to the data controller, and in the case of NHS Scotland originated data to Scottish Government eHealth division.
- I GUARANTEE THAT no publication will appear in any form in which an individual may be identified without the written permission of that individual, and that I will apply appropriate disclosure control when planning publications involving the data requested.
- I UNDERSTAND THAT the Data Controller, and agents acting on its behalf, reserves the right to inspect the data on the sites where it is being processed.

To be signified by the APPLICANT

Name (in Capitals): DINARA GALIYEVA 	Date:27/10/2015

- I DECLARE THAT (the applicant named above) is a *bona fide* worker engaged in a reputable project and that the data he/she asks for can be entrusted to him/her in the knowledge that he/she will conscientiously discharge his/her obligations, including in regard to confidentiality of the data, as stated in the declaration above.

To be signified by the INFORMATION CUSTODIAN named in Section 1.3 above (where the Information Custodian is not the applicant).

Name (in Capitals):SARAH WILD 	Date:27/10/2015

Section 7 - Supporting Evidence

Supporting Evidence *Please read section 7 of the guidance*
Please list each piece of supporting evidence which you have included with your application in the box below – the name of each should clearly indicate what the document/file/reference is about
Application form for data access to Scottish Renal Registry CPHS ethical review form Information Governance Training Certificates for Dinara Galiyeva and Caroline Jackson

Appendix 3

List of terms included within the exploded heading "cardiovascular diseases"

Cardiovascular Diseases [C14]

- Cardiovascular Abnormalities [C14.240]
- Cardiovascular Infections [C14.260]
    - Endocarditis, Bacterial [C14.260.249]
    - Syphilis, Cardiovascular [C14.260.500]
    - Tuberculosis, Cardiovascular [C14.260.750]
- **Heart Diseases [C14.280]**
    - Arrhythmias, Cardiac [C14.280.067]
        - Arrhythmia, Sinus [C14.280.067.093]
        - Atrial Fibrillation [C14.280.067.198]
        - Atrial Flutter [C14.280.067.248]
        - Bradycardia [C14.280.067.319]
        - Brugada Syndrome [C14.280.067.322]
        - Cardiac Complexes, Premature [C14.280.067.325]
        - Commotio Cordis [C14.280.067.441]
        - Heart Block [C14.280.067.558]
        - Long QT Syndrome [C14.280.067.565]
        - Parasystole [C14.280.067.672]
        - Pre-Excitation Syndromes [C14.280.067.780]
        - Tachycardia [C14.280.067.845]
        - Ventricular Fibrillation [C14.280.067.922]
        - Ventricular Flutter [C14.280.067.961]
    - Carcinoid Heart Disease [C14.280.104]
    - Cardiac Conduction System Disease [C14.280.123]
    - Cardiac Output, High [C14.280.142]
    - Cardiac Output, Low [C14.280.148]
    - Cardiac Tamponade [C14.280.155]
    - Cardiomegaly [C14.280.195]
    - Cardiomyopathies [C14.280.238]
    - Endocarditis [C14.280.282]
    - Heart Aneurysm [C14.280.358]
    - Heart Arrest [C14.280.383]
    - Heart Defects, Congenital [C14.280.400]
    - Heart Failure [C14.280.434]
    - Heart Neoplasms [C14.280.459]
    - Heart Rupture [C14.280.470]
    - Heart Valve Diseases [C14.280.484]
    - Myocardial Ischemia [C14.280.647]
    - Myocardial Stunning [C14.280.671]
    - Pericardial Effusion [C14.280.695]
    - Pericarditis [C14.280.720]
    - Pneumopericardium [C14.280.763]

    - Postpericardiotomy Syndrome [C14.280.793]
    - Pulmonary Heart Disease [C14.280.832]
    - Rheumatic Heart Disease [C14.280.874]
    - Ventricular Dysfunction [C14.280.945]
    - Ventricular Outflow Obstruction [C14.280.955]
- Pregnancy Complications, Cardiovascular [C14.583]
- Vascular Diseases [C14.907]
    - Aneurysm [C14.907.055]
    - Angiodysplasia [C14.907.075]
    - Angiomatosis [C14.907.077]
    - Angioedema [C14.907.079]
    - Aortic Diseases [C14.907.109]
    - Arterial Occlusive Diseases [C14.907.137]
    - Arteriovenous Malformations [C14.907.150]
    - Capillary Leak Syndrome [C14.907.218]
    - Cerebrovascular Disorders [C14.907.253]
        - Basal Ganglia Cerebrovascular Disease [C14.907.253.061]
        - Brain Ischemia [C14.907.253.092]
        - Carotid Artery Diseases [C14.907.253.123]
        - Cerebral Small Vessel Diseases [C14.907.253.329]
        - Cerebrovascular Trauma [C14.907.253.535]
        - Intracranial Arterial Diseases [C14.907.253.560]
        - Intracranial Embolism and Thrombosis [C14.907.253.566]
        - Intracranial Hemorrhages [C14.907.253.573]
        - Leukomalacia, Periventricular [C14.907.253.612]
        - Sneddon Syndrome [C14.907.253.774]
        - Stroke [C14.907.253.855]
        - Vascular Headaches [C14.907.253.937]
        - Vasculitis, Central Nervous System [C14.907.253.946]
        - Vasospasm, Intracranial [C14.907.253.951]
    - Colitis, Ischemic [C14.907.286]
    - Compartment Syndromes [C14.907.303]
    - Diabetic Angiopathies [C14.907.320]
    - Embolism and Thrombosis [C14.907.355]
    - Hand-Arm Vibration Syndrome [C14.907.440]
    - Hemorrhoids [C14.907.449]
    - Hemostatic Disorders [C14.907.454]
    - Hepatic Veno-Occlusive Disease [C14.907.460]
    - Hyperemia [C14.907.474]
    - Hypertension [C14.907.489]
    - Hypotension [C14.907.514]
    - Mesenteric Ischemia [C14.907.549]
    - Myocardial Ischemia [C14.907.585]
    - Optic Neuropathy, Ischemic [C14.907.601]
    - Peliosis Hepatis [C14.907.609]
    - Peripheral Vascular Diseases [C14.907.617]
    - Prehypertension [C14.907.653]
    - Pulmonary Veno-Occlusive Disease [C14.907.690]

- Reperfusion Injury [C14.907.725]
- Retinal Vein Occlusion [C14.907.760]
- Scimitar Syndrome [C14.907.780]
- Spinal Cord Vascular Diseases [C14.907.790]
- Splenic Infarction [C14.907.795]
- Stenosis, Pulmonary Vein [C14.907.798]
- Superior Vena Cava Syndrome [C14.907.800]
- Telangiectasis [C14.907.823]
- Thoracic Outlet Syndrome [C14.907.863]
- Varicocele [C14.907.903]
- Varicose Veins [C14.907.927]
- Vascular Fistula [C14.907.933]
- Vascular Neoplasms [C14.907.936]
- Vascular System Injuries [C14.907.937]
- Vasculitis [C14.907.940]
- Vasoplegia [C14.907.946]
- Venous Insufficiency [C14.907.952]

Appendix 4

MEDLINE search strategy (1946 to July Week 2015) excluding records added from August 2015 and separating English and non-English papers

1. (chronic kidney or chronic renal or CKD or impaired renal function or end stage renal disease or ESRD or renal replacement therapy or RRT or dialysis or hemodialysis or haemodialysis or peritoneal dialysis or renal transplantation or kidney transplantation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2. exp renal replacement therapy/ or exp renal dialysis/ or exp kidney transplantation/

3. exp renal insufficiency, chronic/ or exp kidney failure, chronic/

4. 1 or 2 or 3

5. (death or mortality or all- cause mortality or all-cause death or overall mortality or overall death).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6. (cardiovascular mortality or cardiovascular death or cerebrovascular mortality or cerebrovascular death).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7. exp Mortality/

8. exp Cardiovascular Diseases/ or exp Cerebrovascular Disorders/ or cerebrovascular morbidity.mp. or cardiovascular morbidity.mp.

9. 5 or 6 or 7 or 8

10. (cardiovascular risk factors or risk prediction score or risk prediction model).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

11. exp risk factors/

12. exp hypertension/ or exp hypertension, renal/ or hypertension.mp.

13. (Obes$ or overweight or BMI or body mass index or underweight).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

14. exp Obesity/ or exp Overweight/ or exp Body Weight/

15. (anemia or anaemia or target hemoglobin or haemoglobin or iron deficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

16. exp Anemia/

17. (dyslipidemia or dyslipidaemia or hyperlipidemia or hyperlipidaemia or dyslipoproteinemia or dyslipoproteinaemia or abnormal lipid profile or hypercholesterolaemia or hypercholesterolemia or cholesterol or triglycerides).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18. exp dyslipidemias/ or exp hyperlipidemias/

19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. (child* or paediatric or pediatric or teen* or adolescen* or young adult*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

21. exp Child/

22. 20 or 21

23. 4 and 9 and 19 and 22

24. limit 23 to (english language and humans)

25. (201508$ or 201509$ or 20151$ or 2016$ or 2017$).ed.

26. 23 not 25

27. limit 26 to humans

28. limit 27 to english language

29. 27 not 28